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PEER-REVIEWED CONFERENCE REPORT

Clinical data for UC
Novel data and treatment options with tofacinib, ozanimod, vedolizumab and infliximab against ulcerative colitis.

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Editor Dr. M. Löwenberg, Academic Medical Center, The Netherlands

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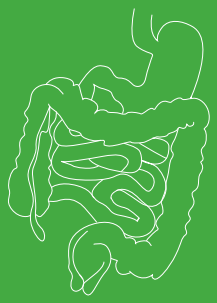

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Letter from the Editor

Dr. Mark Löwenberg

Dear Reader,

From October 29th untill November 1st, the 25th UEG Week took place in Barcelona, the largest European gastroenterology forum that represents a unique platform for collaboration and the exchange of knowledge.
Here, we present the highlights from this congress. Clinically relevant topics have been selected.

I hope that you will enjoy our selection.

With kind regards,

Mark Löwenberg, Gastroenterologist

Biography

Mark Löwenberg is a gastroenterologist trained at the Academic Medical Centre (AMC) in Amsterdam, The Netherlands. He is specialised in inflammatory bowel diseases. In 2000, Löwenberg did a research internship at Harvard Medical School (Dana Farber Cancer Institute). After finishing medical school, he started his PhD in 2003 at the AMC. His research dealt with defining the interactions between cellular signaling pathways in immune cells and therapeutic interventions in inflammatory bowel diseases. Löwenberg completed his fellowship in gastroenterology in March 2012. He is mainly involved in studies concerning the optimisation of treatment strategies for inflammatory bowel disease.

Biomarkers in IBD

At the basis of elucidating the pathophysiology and finding effective therapies for inflammatory bowel disease (IBD)-related disorders are biomarkers. New biomarkers continue to be found, thus improving diagnosis and possible treatment options for IBD.

Inflammation not main cause of chronic symptoms in IBS

Although the role of inflammatory mediators in the pathophysiology of Irritable Bowel Syndrome (IBS) has been widely studied, there is a lack of consistent findings across cohorts. The majority of studies rely on cross-sectional findings which fail to capture the variability of responses over time. Schmidt et al. evaluated if cytokine changes are temporally stable and differences in mucosal and serum cytokines in healthy individuals and IBS patients (constipation predominant; IBS-C and diarrhoea predominant; IBS-D) [1]. To this end, human sigmoid biopsies and serum from age matched healthy and IBS patients with a mean age of 38 years (range 20-59 years, n=15 IBS-C; n=14 IBS-D; n=8 healthy) were obtained. These measurements were repeated after 3-6 months in 8 IBS-C patients, 10 IBS-D patients, and 8 healthy controls. Biopsies were homogenised and the levels of 14 cytokines previously shown to be relevant in IBS (TGF β1, IL-17A, TNFα, IL-10, IL-6, interferon-γ -γ, IL-8, IL-1β, Leptin, IL-22, IL-18, VEGF, MIG, and IL-1RA) were measured in duplicate using ELISA. No significant differences in the temporal variability of mucosal cytokine levels over the two time points were observed when comparing patients with IBS and healthy controls. Interferon-γ was significantly decreased in patients with IBS-C compared to healthy controls (P=0.0005; q=0.007) and TNFα was significantly decreased in patients with IBS-D (P=0.02; q=0.16) and the same trend was seen at both time points. No other cytokines were found to be significantly different in mucosal biopsies. Additionally, there were no significant differences in cytokine levels in the serum among patients with IBS and healthy controls. It was concluded that colonic cytokine levels did not vary over a period of 3-6 months in patients with IBS. The levels of pro-inflammatory cytokines were lower in patients with IBS with stable symptoms which suggests that inflammation may not be the main cause of chronic symptoms in IBS.

Eosinophil-associated cytokines elevated in IBD, especially in ulcerative colitis

Although the pathogenesis of IBD is multifactorial and still not fully elucidated, there is consensus that an impaired immune response – evoked by environmental triggers and/or genetic factors – to the gut microbiota plays a key role. The adaptive immunity seems to be the most important element in the pathogenesis of IBD. However, the inflamed mucosa is also infiltrated by cytokine-rich innate immune cells; their unceasing activation contributes to local and systemic inflammation. Neubauer et al. assessed the circulating eosinophil-associated cytokines and growth factors as differential markers and indicators of mucosal healing in IBD [2]. The study population consisted of 277 individuals: 101 patients with Crohn's disease (CD), 77 with ulcerative colitis (UC), 16 with IBS and 83 healthy controls. Disease severity was assessed using the Crohn's Disease Activity Index (CDAI) for CD and the Mayo score for UC. Additionally, Mayo endoscopic score was applied to evaluate endoscopic disease activity in UC patients. The concentrations of eosinophil-associated cytokines and growth factors (eotaxin, GM-CSF, interferon-γ γ, IL4, IL5, IL8, IL12(p70), IL13, RANTES and TNFα) were measured simultaneously in patient's sera and referred to IBD activity and the levels of high-sensitivity C-reactive Protein (hsCRP). When compared to IBS patients or healthy controls, patients with CD had significantly higher levels of IL5, IL8, IL12(p70), GM-CSF, and TNFα; for UC patients, this was the case for levels of eotaxin, IL4, IL5, IL8, IL12(p70), IL13, GM-CSF, and TNFα. As compared to CD patients, patients with UC had significantly higher levels of eotaxin, IL4, IL5, IL8, and IL1. In turn, the concentrations of hsCRP were significantly higher in CD than UC. Except for IL13, all cytokines and hsCRP positively correlated with CDAI but solely IL12(p70) and hsCRP were significantly higher in patients with active than inactive CD. In UC, a positive correlation with Mayo Disease activity index was observed for hsCRP, GM-CSF, IL12(p70), and interferon-γ -γ and a negative one for IL8. As differential individual markers, eotaxin displayed superior accuracy as an indicator of active UC (71%), followed by hsCRP as an indicator of active CD (66%). The combined assessment of eotaxin, hsCRP and IFNγ had slightly higher accuracy (78%) and allowed for a correct classification of 72% patients. The concentrations of hsCRP, GM-CSF, IFNg, and IL12(p70) were

significantly and positively correlated with the degree of bowel inflammation, expressed as Mayo endoscopic subscore. Of these, a drop in GM-CSF had superior accuracy as an indicator of mucosal healing (91%), allowing for a correct classification of 87% of patients. IL5, IL8, IL12(p70), TNF, and GM-CSF were significantly higher in both CD and UC than in IBS. Of these, IL8 had superior accuracy in differentiating IBS and IBD (91%), allowing for a correct classification of 93% of patients. The researchers concluded that eosinophil-associated cytokines are elevated in IBD, more pronouncedly in UC, and may support the differential diagnosis of IBD and aid in monitoring of mucosal healing.

CEACAM6 possible biomarker in CD

Enterobacteria, especially adherent and invasive *E. coli* (AIEC), are suspected to play a key role in CD. These bacteria are able to highly adhere to the ileal mucosa of CD patients through the carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) receptor. The correlation between the level of CEACAM6 in the saliva and the level of CEACAM6 in the ileum in CD patients was assessed to define the best threshold of CEACAM6 in the saliva to detect overexpression of ileal CEACAM6. Researchers also tried to identify non-invasive biomarkers of AIEC infection. This was done in a prospective multicentre study with 102 patients requiring ileocoloscopy. Clinical and endoscopic data were collected on the day of colonoscopy. Blood samples, stool samples (before bowel cleansing), saliva and ileal biopsies from healthy and ulcerated areas were also collected. Ileal CEACAM6 level did not depend on disease severity or the site of biopsies and there was no difference in healthy or ulcerated zone. The median level of CEACAM6 from saliva was 3837 pg/mg [1889; 7338]. There was a positive correlation between the levels of CEACAM6 in saliva and CEACAM6 in the ileum (P=0.47; P<0.0001) The cut-off value of 3800 pg/mg demonstrated the best performances to detect ileal CEACAM6 overexpression with substantial specificity (76.0%) and positive predictive value (87.5%). The number of enterobacteria was increased in CD patients with prior intestinal resection (562 vs. 116 pg/mg, P=0.03). Interestingly, the number of enterobacteria was also increased in AIEC positive-patients (640 vs. 60 pg/mg, P=0.004). The best threshold of enterobacteria in the ileum was determined to detect the presence of ileal AIEC bacteria; an area under the curve of 0.70 was found. The cut-off value of 60 colony-forming unit (CFU)/biopsy, demonstrated the best performances to detect the presence of ileal AIEC bacteria. The number of enterobacteria associated to ileal mucosa (cut-off value >60 CFU/biopsy) strongly predicted the presence of AIEC, and is a reliable test for AIEC screening with high negative predictive value (94.1%) and high sensitivity (91.7%). It was concluded that CEACAM6 measurement in the saliva is feasible, non-time-consuming and non-invasive. It could be a reliable test to detect the overexpression of CEACAM6 in the ileum from CD patients, and could then be proposed as a non-invasive biomarker to select patients who might benefit from anti-adhesive therapies. In addition, researchers identified that the number of enterobacteria associated to the ileum is a convenient and reliable test to screen CD patients for AIEC bacteria [3].

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Mucosal Healing

Mucosal healing is associated with positive outcomes in patients with IBD and is increasingly used as an endpoint in clinical trials. Various (new) therapeutic agents have shown to positively affect mucosal healing.

Golimumab and mucosal healing: real-life data

Although golimumab is registered for moderate-to-severe UC, there is little data on the use of golimumab in daily clinical practice. Especially with regard to predictors that influence favourable outcomes, much is still unknown. Bossuyt et al. evaluated the mid-term outcome of golimumab in patients with moderate-to-severe UC as well as determining predictors of favourable outcomes. This was done by evaluating patients included in the SMART study for their mid-term outcome [1]. Demographic data, disease characteristics and medical history were recorded

retrospectively. Data on disease activity based on total mayo score, previous and concomitant medication, golimumab dosing, mucosal healing (mayo 0 or 1), AEs, colectomy, hospitalisation) and biomarkers (CRP), faecal calprotectin, haemoglobin and albumin) were collected at baseline, week 2, 6, 14, 26 and 52. The primary endpoint was steroid-free golimumab continuation at week 26. Of a total of 100 patients, 8 had to be excluded due to low baseline disease activity, misdiagnosis, and loss of follow-up. The most important patient characteristics are described in Table 1.

Table 1 Patient characteristics [1]

Patient characteristics	Included patients n=92
Gender • Male • Female	 58% 42%
Median age	41.0 years
Median disease duration	5.0 years
Active smoker	4%
Extensive colitis	25%
Endoscopic Mayo score 3 at baseline	38%
Median (interquartile range) baseline Mayo score	9 (8-10)
Previously failed immunomodulators	76%
Anti-TNF naïve	87%

Golimumab was started in combination with immuno-modulators and steroids in 38% and 64%, respectively. The median interquartile range follow-up on golimumab therapy was 36 (12-106) weeks. Twenty-six weeks after golimumab induction, 41% was steroid-free and still on golimumab (6 patients of those required golimumab dose optimisation). Short-term mucosal healing at week 14 was observed in 52% of patients. In a multivariate analysis, only concomitant systemic steroids (P=0.044) were predictive of short-term mucosal healing. Patients with short-term mucosal healing more frequently achieved the primary endpoint [67% vs. 29%, OR 4.86 (95%CI 1.43-16.50), P=0.011]. During a median interquartile range follow-up of 26 (23-30) months, 78% needed a therapeutic intervention and 63% discontinued golimumab. Short-term mucosal healing was significantly associated with intervention free survival (P=0.030) and prolonged treatment of golimumab (P=0.002). These real-life data confirm effectiveness of golimumab on the mid-term in moderate-to-severe UC, although therapeutic interventions are needed frequently.

Good diagnostic ability of artificial intelligence in classifying endocytoscopic images

Recent studies suggest that histological remission might be an important treatment goal in UC. However, there is a discrepancy between histological remission and mucosal healing. Already, two useful aspects of endocytoscopy have been reported. Firstly, EndoCytoscopic Narrow-Band Imaging (EC-NBI) finding of capillaries in the rectal mucosa is strongly correlated with histological inflammation and can aid in the differential diagnosis between active and inactive UC [2]. Secondly, a computer-aided diagnosis system in diagnosis of EC images of colorectal lesions has an interesting potential interpretation of these modalities is difficult for novices [3]. The aim of this study was to develop a new computer-aided diagnosis system for the histological remission in UC, with use of EC combined with NBI mode. Histological assessment was based on Geboes index. Geboes index 3.0 and absence of basal plasmacytosis was considered as histological remission, while Geboes index 3.0 or presence of basal plasmacytosis was as active. The algorithm of this computer-aided diagnosis system was programmed based on texture analysis, which can quantify the pattern of endoscopic image and vessel features. A support vector machine was used as a classifier for two-category diagnostic output (histological remission or active status). A total of 1,935 EC images (histological remission, n=1,042; active status, n=893) were used for the machine-learning process. The overall accuracy to distinguish histological remission from active status was assessed by using leave-one-out cross validation. In this validation, a randomly selected one EC image was evaluated by using the developed computer-aided diagnosis system, which was trained by using the remaining 1,934 images. According to the leave-one-out cross validation which was repeatedly calculated for 1,935 times, the average accuracy of the developed computer-aided diagnosis system for identification of histological remission was 81.7%. The accuracy with high confidence (probability ≥90%) was 98.9%. The high confidence rate was 32.4%. Thus, the diagnostic ability of artificial intelligence in classification of EC images for the assessment of histological activeness of UC was substantially good, although it was a tentative model. Higher accuracy could be expected with greater numbers of images used for training [4].

Filgotinib induces mucosal healing in CD

Filgotinib – a selective Janus kinase (JAK)1 inhibitor – has shown efficacy in a phase 2 study in CD patients. [5] A post-hoc analysis explored the correlation between histologic and endoscopic disease activity at baseline and following filgotinib induction therapy, by comparison of the total ileal Global Histology Activity Score (IGHAS), colonic GHAS (CGHAS) score or IGHAS/CGHAS activity sub-scores (a; activity items: presence of epithelial damage, polymorphonuclear leukocytes in lamina propria, neutrophils in epithelium, erosion or ulceration, granuloma) vs. total ileal Simplified Endoscopic Score for CD (ISES-CD), colonic SES-CD (CSES-CD) score or ISES-CD/CSES-

CD ulcer sub-scores (u; sum of size and % affected surface) [6,7]. A total of 174 CD patients were randomised 3:1 to receive 200 mg filgotinib or placebo once a day (QD) for 10 weeks [7]. Intestinal biopsies were collected at baseline and Week 10 from the most affected areas of each predefined bowel segment (ileum, ascending, transverse, descending, sigmoid colon and rectum). Baseline values were comparable across treatment groups, although CGHAS and CSES-CD were numerically higher in the placebo group. Following 10 weeks of treatment with filgotinib 200 mg, histologic measures of colonic mucosal inflammation (CGHAS and aCGHAS) were significantly improved and were coupled with macroscopic changes in both CSES-CD and uCSES-CD. Changes in histology score for ileal segments were numerically greater after filgotinib treatment vs. placebo. Histology total and sub-scores were significantly associated with total and endoscopic ulcer sub-scores at both time points. Moreover, they were more pronounced when looking into the colonic segments vs. the ileal segments (Table 2).

Table 2 Histologic scores of inflammation [7]

	Baseline	Week 10
IGHAS vs. ISES-CD	Corr = 0.62 (P<0.001)	Corr = 0.65 (P<0.001)
aIGHAS vs. uISES-CD	Corr = 0.53 (P<0.001)	Corr = 0.43 (P<0.001)
CGHAS vs. CSES-CD	Corr = 0.80 (P<0.001)	Corr = 0.77 (P<0.001)
aCGHAS vs. uCSES-CD	Corr = 0.77 (P<0.001)	Corr = 0.70 (P<0.001)

It was concluded that improvement in endoscopic disease activity by filgotinib treatment is paralleled by improved histological scores. In line with previous findings with anti-TNF agents, colonic mucosa is more prone to improve as compared to ileal disease [8-10]. Spontaneous reduction in histological disease activity in patients receiving placebo were not observed [11].

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Ulcerative Colitis

Novel treatment options for UC: JAK1 inhibitors and integrin antagonists.

Efficacy and safety data with tofacitinib

Efficacy and safety of tofacitinib – an oral, small molecule that inhibits JAK1 – was effective as induction and maintenance therapy in Phase 3, randomised, placebo-controlled studies in patients with moderate-to-severe UC [1,2]. In a long-term extension study, safety and efficacy data were assessed up to 3 years of treatment. This study consisted of patients who had completed or demonstrated treatment failure in OCTAVE Sustain, or who were non-responders after completing OCTAVE Induction 1 or 2. Eligibility for this study was determined based on week 8 data from OCTAVE induction 1 and 2, or week 52 data (for completers) or early termination data from OCTAVE sustain. Patients who were in remission at week 52 of OCTAVE sustain were assigned to tofacitinib 5 mg twice daily (BID); all others were assigned 10 mg BID. In total, 914 patients (5 mg BID: 17.1%; 10 mg BID: 82.9%) received at least one dose of study drug, of whom 41.7% discontinued (10.9% in the tofacitinib 5 mg BID group and 48.0% in the tofacitinib 10 mg BID group). Reasons for discontinuations included AEs; 2.6% and 2.5%, respectively, and insufficient clinical response (at data cut-off, July 2016, cumulative: 4.5% and 36.4%, respectively). An overview of all-causality AEs is shown in Table 3. The proportion of patients in remission - defined by Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0 – over time for tofacitinib 5 mg and 10 mg is shown in Figure 1 [3].

Table 3 All-causality AEs [3]

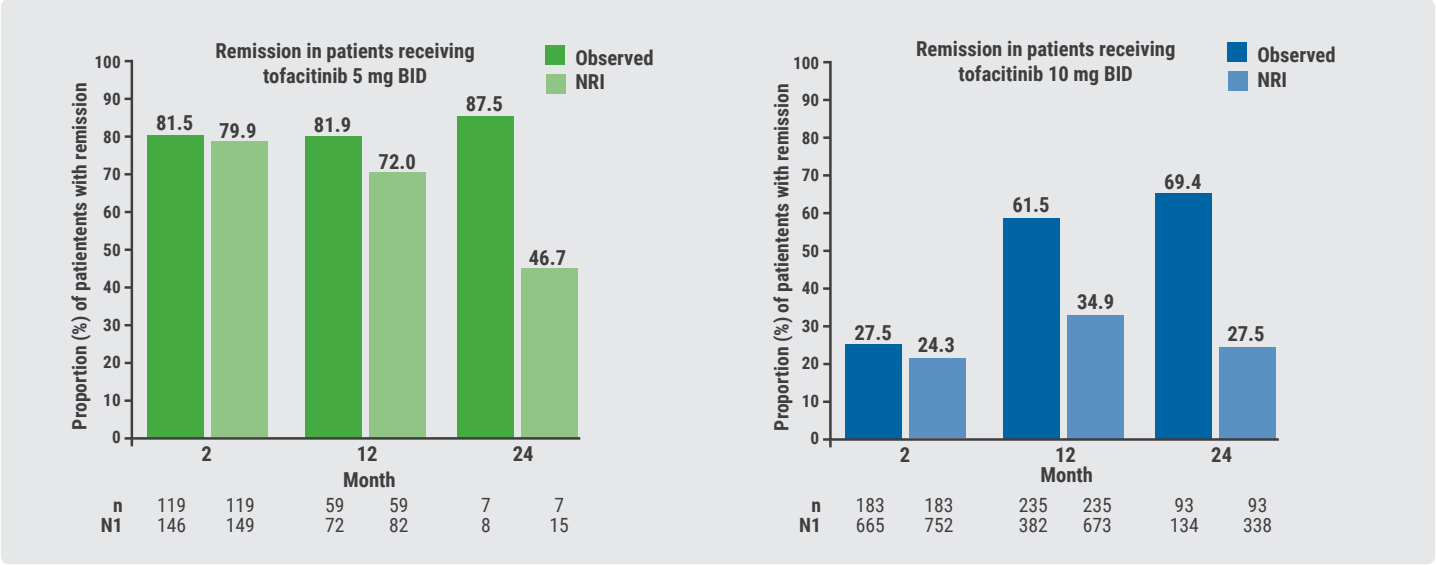
	Tofacitinib 5 mg BID (n=156)	Tofacitinib 10 mg BID (n=758)	Tofacitinib Total (n=914)
All-causality TEAEs, n (%)			
AEs	101 (64.7)	562 (74.1)	663 (72.5)
SAEs	11 (7.1)	84 (11.1)	95 (10.5)
Severe AEs	7 (4.5)	64 (8.4)	71 (7.8)
GI AEs	38 (24.4)	270 (35.6)	308 (33.7)
Infection AEs	62 (39.7)	317 (41.8)	379 (41.5)
All-causality TEAEs by preferred term occuring in ≥10% of patients, n (%)			
Worsening UC AE	19 (2.2)	105 (13.9)	124 (13.6)
Nasopharyngitis AE	18 (11.5)	110 (14.5)	128 (14.0)

Most patients appeared to remain in remission through month 12 for tofacitinib 5 mg BID (the number of patients was small by month 24, which is considered a limitation of the study); for tofacitinib 10 mg, this was generally stable through month 24. These findings showed that tofacitinib 5 and 10 mg BID demonstrated a consistent safety profile. The most frequent AE leading to discontinuation was worsening of UC, whereas the two most frequent TEAE system organ classes in both dose groups were 'infections and infestations' and 'gastrointestinal disorders'; the two most frequent TEAEs by preferred term were nasopharyngitis and worsening of UC. No new safety concerns emerging compared with earlier tofacitinib studies in rheumatoid arthritis. Efficacy results for remission and mucosal healing from this study support long-term efficacy with tofacitinib 5 and 10 mg BID through to month 24 [3]. Further research on safety with this new drug in patients with moderate-to-severe UC, based on integrated analyses of one phase 2 (8 weeks) and two phase 3 induction (8 weeks each) studies, one phase 3 maintenance (52 weeks) study and one long-term extension study which is still ongoing, showed no unexpected safety signals. These results showed an overall acceptable safety profile for tofacitinib 10 mg BID induction therapy and for tofacitinib 5 and 10 mg BID maintenance therapy in UC patients [4].

Efficacy and safety data with ozanimod

Ozanimod – an oral, once-daily immunomodulator that selectively targets sphingosine-1-phosphate receptors 1 (S1PR1) and S1PR5 – has demonstrated clinical efficacy in UC treatment as induction and maintenance therapy [5]. The objective of the open-label extension study (TOUCHSTONE trial) was to evaluate long-term efficacy and safety of daily 1 mg ozanimod in patients with moderate-to-severe UC who had initially participated in the TOUCHSTONE trial for up to 32 weeks. A total of 197 patients were randomised (1:1:1) and treated with daily ozanimod 0.5 mg (n=65), 1 mg (n=67), or placebo (n=65) in the TOUCHSTONE trial. Of the initial 197 patients randomised, 86% entered the open-label extension and received daily ozanimod 1 mg. The mean age was 40.4 years, 57.6% was male and the mean number of years since UC diagnosis was 5.9 years. As of the data cut-off in March 2017, 58.8% had efficacy evaluations reported through week 92. Of these 100 patients, 55.3% had received ozanimod 1 mg/day in the open-label extension for ≥2 years. Efficacy data were reported as observed through week 92 and safety included all events through the data cut-off. At entry into the open-label extension, the partial mayo Score for patients

Figure 1 Proportion of patients with remission over time [3]



nri = non-response imputation

on placebo, ozanimod 0.5 mg, and 1.0 mg was 4.6, 4.5, and 3.3 respectively, which improved significantly by open-label extension week 8 (–2.3, –1.9 and –1.1), with the greatest improvement reported in patients who had received placebo or ozanimod 0.5 mg in the TOUCHSTONE trial. At the week 92 visit in the open-label extension, 91.0% had little or no active disease based on the physician global assessment (0 or 1), 97.0% had little or no blood in their stools (rectal bleeding sub-score 0 or 1), 86.0% had no blood in their stools (rectal bleeding sub-score 0). AEs and serious AEs were reported in 50.0% and 11.1% of patients respectively. The most common AEs (>2.0%) during open-label extension were UC flare, anaemia, nausea, upper respiratory tract infection, nasopharyngitis, back pain, arthralgia, headache, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation and hypertension. The only serious AEs in ≥2 patients were anaemia, and UC flare. ALT and AST >3x upper limit of normal occurred in 2.9% of the 170 patients in the open-label extension. All elevations were asymptomatic, <5x upper limit of normal, transient, and resolving while receiving continued treatment. It was concluded that long-term treatment with ozanimod continues to be safe and is well tolerated with evidence of durable efficacy [6].

Early symptomatic improvement with vedolizumab

Vedolizumab – an α4β7 integrin monoclonal antibody for the treatment of moderately-to-severe active UC – has shown to achieve long term clinical remission and mucosal healing in patients with moderately to severely active UC [7]. Rapid symptomatic relief of rectal bleeding and stool frequency remain important treatment goals for patients and are key indicators for physicians in clinical practice. Feagan et al. aimed to characterize early symptomatic response with vedolizumab, specifically evaluating the timing of rectal bleeding and stool frequency improvement. Symptomatic improvement with vedolizumab was assessed through a post hoc analysis of GEMINI 1 data. Patients with active UC were randomised to receive double-blind placebo or vedolizumab at weeks 0 and 2 during the 6-week induction phase (intent-to-treat population). Mayo clinic sub-scores of stool frequency and rectal bleeding were evaluated at 0, 2, 4, and 6 weeks. Mean sub-scores and mean percent change from baseline were reported for the overall population and in those who were tumour necrosis factor antagonist (anti-TNF) naïve. The percentages of patients who reached stool frequency sub-score ≤1 and/or rectal bleeding sub-score of 0 were also determined. In anti-TNF-naïve patients (placebo n=76; vedolizumab, n=130), greater percentage decreases in mean stool frequency sub-scores from baseline were observed with vedolizumab than with placebo, reaching statistical significance at weeks 4 and 6 as indicated by the non-overlapping 95% confidence intervals (CI). The same trends were observed in the overall population (placebo n=149; vedolizumab n=225) without reaching statistical significance.

Similarly, a numerically greater percentage decrease from baseline in rectal bleeding sub-score was observed with vedolizumab than with placebo, reaching statistical significance at week 6 in both anti-TNF-naïve and overall populations. Significantly larger percentages of patients overall achieved stool frequency sub-score ≤1 or rectal bleeding sub-score of 0 with vedolizumab than with placebo at week 6 and as early as week 2 among the anti-TNF-naïve population. A composite of stool frequency sub-score ≤1 and rectal bleeding sub-score of 0 was achieved in a significantly greater percentage of patients with vedolizumab than placebo at all-time points. Although researchers pointed out that the interpretation of these exploratory analyses is limited by the relatively small sample sizes, symptomatic improvements were achieved with vedolizumab as early as week 2. This included a combined reduction in stool frequency and elimination of rectal bleeding. There were greater differences from placebo observed in anti-TNF-naïve patients. Taken together, these results highlight the rapid onset of vedolizumab in UC. However, assessing clinical efficacy at week 14 and beyond for those who exhibit a more gradual response should be used to inform clinical practice [8].

Bridging strategy with calcineurin inhibitor to vedolizumab

Although vedolizumab has shown efficacy in UC, patients with acute severe UC have been excluded from pivotal trials and the use of vedolizumab in acute steroid-refractory patients is limited [7]. In patients with steroid-refractory UC, prior thiopurine and anti-TNF failure or intolerance, a combination therapy between a calcineurin inhibitor (ciclosporine/tacrolimus) as an induction therapy associated with vedolizumab as maintenance could be an interesting approach. The aim of the study by Pellet et al. was to assess efficacy and safety of the bridging strategy with a calcineurin inhibitor to vedolizumab in patients with steroid-refractory acute severe UC or non-severe UC. This was assessed by conducting a retrospective cohort study in 12 French referential centres, including all consecutive patients who have been treated for an active steroid-refractory UC (acute severe UC or non-severe UC) by a calcineurin inhibitor (ciclosporin or tacrolimus) as induction therapy and vedolizumab as maintenance therapy. Inclusion was defined by the day of the first vedolizumab infusion. Outcomes were survival without

colectomy, survival without vedolizumab discontinuation, clinical response and remission rates at weeks 6 and 14, predictors of survival without colectomy and safety. A total of 39 patients (23 females, mean age 32 years) were recruited and received a calcineurin inhibitor - ciclosporin in 37 and tacrolimus in 2 - and vedolizumab with a median interval of 7 days. The median follow-up duration was 10.8 months. Regarding previous medications, 85% patients had failed to respond to conventional immunosuppressants (thiopurines and/or methotrexate) and they were contra-indicated in 11%. Moreover, 92% patients had failed to at least one anti-TNF agent, while these drugs were contra-indicated in 8%. At inclusion, 76% of patients had pancolitis, 61% had already presented an acute severe UC; median CRP was 12.9 mg/L; median lichtiger score and total mayo Score were 9 and 10, respectively. At 12 months, 68% achieved survival without colectomy (95% CI: 53%-84%), while 44% achieved survival at 12 months without vedolizumab discontinuation (95% CI 27%-61%). Clinical remission (partial mayo score <3) and response (partial mayo score decreases of >2 points and 30% from inclusion) rates at week 6 and week 14 were 46%/64% and 38%/56%, respectively. In a multivariate analysis, factors associated with colectomy were outlined (Table 4).

Table 4 Factors associated with colectomy (multivariate analysis) [9]

Factor at inclusion	HR	95%CI	*P*
Male gender	7.94	0.02-0.49	0.005
Age >32 years	13.16	2.27-76.26	0.004
Concomitant IS	9.59	1.13-81.60	0.039
Haemoglobin >11.2 g/dL	7.29	1.54-34.40	0.012

With regard to safety, 4 AEs occurred, 3 of which were transient kidney failure, leading to ciclosporin withdrawal in one case, and 1 patient had *Campylobacter* colitis. No deaths were observed. It was concluded that in steroid-refractory UC, a bridging strategy combining a calcineurin inhibitor with vedolizumab was safe and effective, with a one-year survival without colectomy of 68% and drug persistence of 44%. Such an approach could be considered in patients with acute severe UC and non-severe UC refractory to conventional therapies, including anti-TNF [9].

Delay in infliximab onset and spacing is a predictor for relapse post-spacing

Infliximab has been around a long time in the IBD field but to date, there is no clear guideline regarding withdrawal of anti-TNF agents. The majority of IBD patients are treated with infliximab for the long term. An alternative to withdrawal of infliximab may be the spacing of infliximab infusion interval. This strategy was only evaluated in a large prospective controlled trial in rheumatoid arthritis patients with interesting results: tapering was not equivalent to maintenance strategy, resulting in more relapses without impacting structural damage progression [10]. Dufour et al. evaluated the effect of a spacing of infliximab-infusion interval on the maintenance of clinical remission in IBD patients. The secondary aims of this study were to evaluate the occurrence of allergic reactions to infliximab after spacing and efficacy of infliximab intensification after clinical relapse. This was done through a retrospective multicentre French national cohort including all IBD patients treated with infliximab who were in clinical remission according to the referring physician and had a spacing of their infusion interval over 9 weeks for at least two consecutive infusions. Clinical relapse after spacing according to referring physician leading to infliximab intensification, was considered as primary endpoint. Clinical efficacy of infliximab intensification after spacing and occurrence of drug reactions were also monitored. A total of 89 patients were included in the study (CD n=61; UC n=28)). Median delay between infliximab introduction and spacing was 35.6 months (interquartile range: 17.6-64). A total of 39% of patients were already treated with an immunosuppressive drug (thiopurine or methotrexate) at the time of infliximab spacing. Maximum infusion interval spacing was of 13 weeks and 46% had infusion interval spacing ≥12 weeks. Of note, no trough levels were available prior to spacing, and no information was provided with regard to anti-drug antibody levels. Cumulative probability of clinical relapse free survival after spacing was 82.7% ±4.1 and 72.6% ±4.9 at 1 and 2 years, respectively. All IBD patients with a clinical relapse after spacing had an intensification of infliximab therapy (n=27) with a clinical response in 89% of patients. Only 1 patient had to withdraw from infliximab therapy after a clinical relapse, caused by an infliximab-related allergic reaction which occurred 3 years after spacing. Regarding clinical relapse, the median delay between infliximab introduction and spacing of infusion interval, was significantly shorter in IBD patients with clinical relapse, compared to patients without clinical relapse (22.9 months (interquartile range: 13.3-42) vs. 41.3 months (interquartile range: 22.5-67.1), respectively, P=0.027). For CD patients, in univariate analysis, a delay >4 years between infliximab introduction and spacing was significantly associated to the maintenance of clinical remission after spacing (RR=0.26; CI 95%: 0.07-0.89, P=0.032). For UC patients, radiologic inflammatory activity before spacing was associated to clinical relapse after spacing (RR=13.9; CI 95%: 1.24-157.1, P=0.033). In multivariate analysis, a delay >4 years between infliximab introduction and spacing (RR 0.36,

CI 95%: 0.19-0.68, P=0.002), concomitant treatment with an immunosuppressant (RR=0.31; CI 95%: 0.11-0.85, P=0.022) and penetrating phenotype (RR=0.57; CI 95%: 0.34-0.97, P=0.039) were significantly associated to the maintenance of clinical remission after spacing in CD patients. Thus, after spacing of infliximab infusions over 9 weeks more than 70% of IBD patients remained in clinical remission over two years. Only one patient stopped infliximab for allergic reaction after clinical relapse and infliximab intensification. A short delay between infliximab introduction and spacing seems to be a good predictive factor of clinical relapse after spacing, at least in CD. The collection and analysis of data from a larger national cohort is ongoing [11].

Targeting CHST15 might lead to mucosal healing and clinical remission

It has been previously shown that carbohydrate sulfotransferase 15 (CHST15), which biosynthesises sulfated matrix glycosaminoglycans, is an important regulator of experimental colitis and gut fibrosis in UC. Atreya et al. evaluated efficacy of double-stranded RNA oligonucleotide STNM01, a specific blocker of CHST15, in refractory UC patients. In a randomised, double-blind, placebo-controlled phase 2a trial, 24 patients with moderate-to-severe UC were randomised to receive a single endoscopic submucosal injection of 25 nM, 250 nM STNM01 or placebo. The results demonstrated that the primary endpoint, mucosal healing at weeks 2 or 4 was achieved by 62.5% in the STNM01 (250 nM) group compared to 28.6% in the placebo group (P=0.018). Clinical remission at these time points was reached by 50.0% in the STNM01 (250 nM) and 14.3% in the placebo groups (P=0.050). There was significant histological improvement according to the Geboes score in the STNM01 (250 nM) group (P<0.01). There were no statistical differences between the lower dose STNM01 (25 nM) and placebo groups. STNM01 application was well tolerated and immunostaining demonstrated significant inhibition of CHST15 expression in STNM01 (250 nM) treated patients. Functionally, STNM01 inhibited sulfation of L-selectin ligand on inflammation-associated high endothelial venule-like vessels, suppressed hydrogen sulfide-producing enzymes and inhibited pre-established fibrosis. In conclusion, these are very interesting findings demonstrating that CHST15 targeting by submucosal injection of CHST15 blocker STNM01 induces mucosal healing and clinical remission in UC patients. Local application of STNM01 would thus be a unique novel therapeutic approach for reversal of tissue remodeling in refractory UC [12].

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Crohn's Disease

Despite different treatment modalities, CD remains a complex condition which often not only affects clinical aspects of the disease, but also patients' quality of life (QoL). With new therapeutic strategies – such as the treat-to-target concept for early disease – significant improvements in both aspects of CD are underway.

Long-term treatment adalimumab well tolerated and independent of age

The global post-marketing observational PYRAMID registry assessed long-term safety and efficacy of adalimumab in routine clinical practice in patients with moderately-to-severely active CD. Patients were enrolled in the registry if they were newly prescribed adalimumab or currently receiving adalimumab treatment, according to the local product label. They were followed for up to 6 years. An analysis by d'Haens and colleagues assessed long-term safety of adalimumab for different age subgroups (<40, 40-59, and ≥60 years) at registry enrolment (baseline). Registry treatment-emergent AEs, defined as any event with onset on/after first dose of adalimumab in the registry up to 70 days after last adalimumab injection were reported as events per 100 patient-years. A total of 5,025 patients in the registry received at least one dose of adalimumab and were included in the analysis. Baseline characteristics are summarised in Table 5.

Table 5 Baseline characteristics of patients [1]

Age group	%	Female	Median age	Median CD duration	Cumulative registry adalimumab exposure
<40 years	59.3%	57.1%	29.0 years	7.0 years	9,681.1 patient-years
40-59 years	34.2%	57.8%	47.0 years	13.0 years	6,009.3 patient-years
≥60 years (≥75 years)	6.5% (7.0%)	52.9%	64.0 years	13.5 years	990.0 patient-years

Approximately 46-52% of patients were receiving adalimumab monotherapy (without immunomodulators or corticosteroids) at baseline across the age subgroups. Similar rates of registry treatment-emergent serious infections and opportunistic infections were observed across the younger age subgroups, but were numerically higher in the ≥60 years subgroup. Rates of any registry treatment-emergent malignancies and non-melanoma skin cancer were likewise significantly higher in older patients (aged ≥60 years at baseline). There was no event of lymphoma reported in the subgroup of patients aged ≥60 years at baseline; however, during the follow-up in the registry, 3 patients classified in the 40-59 years at baseline age group were diagnosed with lymphoma when they were ≥60 years of age. No patients in the ≥60 years group reported active/latent tuberculosis. It was concluded that long-term treatment with adalimumab was well tolerated in patients with moderately-to-severely active CD, irrespective of patient age. The rate of exposure-adjusted registry treatment-emergent AEs (per 100 patient-years) was generally higher in older (≥60 years) compared to younger patients (<60 years); however, no new safety signals were identified in this age group [1].

Combined adalimumab and immunomodulatory treatment significantly increased retention of adalimumab

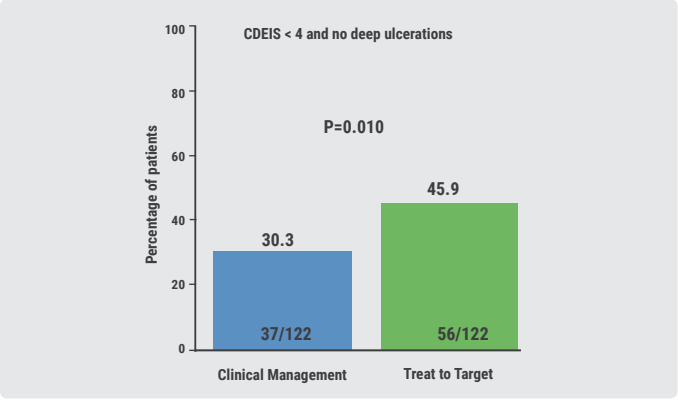
As the benefits of combination therapy with adalimumab and immunomodulators for CD patients is still open for debate, Tanaka et al. aimed to investigate the usefulness of combination therapy with adalimumab and immunomodulators. They based their research on the long-term retention rate of those who participated in the ADJUST study. The ADJUST study was a retrospective cohort study conducted performed in 41 institutions in Japan. Data were retrospectively collected from CD patients who had received at least one induction dose of 160 mg of adalimumab between October 2010 and December 2013. Patients with active CD who received adalimumab for induction of remission were included, while those with inactive CD who started on adalimumab for prevention of postoperative recurrence or for unknown reasons were excluded. A total of 970 patients (median age 33.6 years; 31% female) were included in the study. The median duration of CD was 7.5 years. A total of 43% of patients had undergone at least 1 intestinal resection. Median CRP and albumin levels were 0.90 mg/dL and 3.7 g/dL, respectively. Concomitant treatment with immunomodulators and prednisolone was administered to 37% and 16% of the patients, respectively. A total of 49% of patients had been previously treated with infliximab. The 1-, 2-, 3- and 4-year cumulative retention rates of adalimumab were 78%, 69%, 62% and 58%, respectively. In the multivariate Cox regression analysis, female sex, perianal disease, lower

albumin levels, concomitant treatment with prednisolone and previous infliximab use, were identified as independent predictors for discontinuation of adalimumab. Contrarily, concomitant treatment with immunomodulators was a prognostic factor for higher retention rate of adalimumab. According to the stratified analyses, combination therapy with adalimumab and immunomodulators, significantly improved the cumulative retention rates in patients with CRP levels of ≥4.00 mg/dL and those receiving concomitant treatment with prednisolone, especially for patients previously treated with infliximab. These data suggested that combination therapy of adalimumab and immunomodulators significantly increased retention of adalimumab [2].

Treat-to-target improves outcomes in early disease

The concept of 'treat-to-target' implies that close serial monitoring of patients with CD using inflammatory biomarkers, such as serum CRP and faecal calprotectin, assists in timely treatment escalation in order to improve patients' outcome. CALM, a prospective, open-label, multicentre, active-controlled, phase 3 study, assessed the benefit of treat-to-target vs. standard clinical management in CD patients. The study was conducted in 22 countries at 74 hospitals and evaluated adult patients (aged 18-75 years) with active endoscopic CD (Crohn's Disease Endoscopic Index of Severity [CDEIS] >6; sum of CDEIS sub scores of >6 in one or more segments with ulcers), a Crohn's Disease Activity Index (CDAI) of 150-450 depending on dose of prednisone at baseline, and no previous use of immunomodulators or biologics. Patients were randomly assigned at an 1:1 ratio to a tight control or conventional management group, stratified by smoking status (yes or no), weight (<70 kg or ≥70 kg), and disease duration (≤2 years or >2 years) after 8 weeks of prednisone induction therapy, or earlier if they had active disease. In both groups, treatment was escalated in a stepwise manner, from no treatment, to adalimumab induction, followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. This escalation was based on meeting treatment failure criteria, which differed between groups (tight control group before and after random assignment: faecal calprotectin ≥250 µg/g, CRP ≥5mg/L, CDAI ≥150, or prednisone use in the previous week; clinical management group before random assignment: CDAI decrease of <70 points compared with baseline or CDAI >200; clinical management group after random assignment: CDAI decrease of <100 points compared with baseline or CDAI ≥200, or prednisone use in the previous week). De-escalation was possible for patients receiving weekly adalimumab and azathioprine or weekly adalimumab alone if failure criteria were not met. The primary endpoint was mucosal healing (CDEIS <4) with absence of deep ulcers 48 weeks after randomisation. Between Feb 2011, and Nov 2016, 244 patients (mean disease duration: clinical management group, 0.9 years; tight control group, 1.0 year) were randomly assigned to monitoring groups (n=122 per group). A total of 24% of patients in the clinical management group and 26% of patients in the tight control group discontinued the study, mostly because of AEs. A significantly higher proportion of patients in the tight control group achieved the primary endpoint at week 48 than in the clinical management group (Figure 2).

Figure 2 Primary endpoint at 48 weeks after randomisation [3]

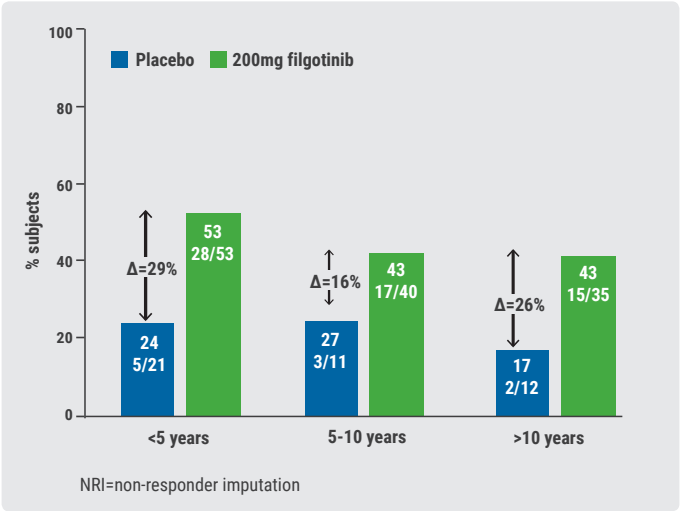


Furthermore, 86% of patients in the tight control group and 82% of patients in the clinical management group reported treatment-emergent AEs; no treatment-related deaths occurred. The most common AEs were nausea (17%), nasopharyngitis (15%), and headache (15%) in the tight control group, and worsening CD (29%), arthralgia (16%), and nasopharyngitis (15%) in the clinical management group. The researchers pointed out that CALM is the first study to show that timely escalation with an anti-TNF therapy on the basis of clinical symptoms combined with biomarkers in patients with early CD results in better clinical and endoscopic outcomes than symptom-driven decisions alone. A significantly higher proportion of patients in the tight control group achieved the primary endpoint at week 48 (46%) than in the clinical management group (30%), with a Cochran–Mantel–Haenszel test-adjusted risk difference of 16.1% (95% CI 3,9-28.3; P=0.010). Future studies should assess the effects of such a strategy on long-term outcomes such as bowel damage, surgeries, hospital admissions, and disability [3].

Efficacy of filgotinib is independent of disease duration and location

A post-hoc analysis of the phase 2 FITZROY study suggested that inhibition of JAK1 with filgotinib in patients with CD is inducing numerically higher clinical remission rates compared to placebo, independent of disease duration or location. A 20-week phase 2 study evaluated the efficacy and safety of filgotinib in patients with active CD. The primary endpoint (CDAI remission at week 10) was met with an acceptable safety profile [4]. In this post-hoc analysis, the effect of disease duration and location has been assessed on the primary endpoint. A total of 172 patients with moderate-to-severely active CD (CDAI: 220-450) and ulcerations confirmed by centrally read endoscopy, were randomised 3:1 to receive 200 mg filgotinib or placebo QD for 10 weeks. Immunosuppressants were discontinued prior to treatment initiation but corticosteroid-treated patients remained stable until week 10. Patients naïve to anti-TNF therapy as well as patients previously exposed to anti-TNF with no response or loss-of-response were included. Clinical remission at week 10 was analysed by disease duration (<5 years, 5-10 years and >10 years) and historical location (ileal, ileo-colonic, colonic). Baseline disease characteristics were similar in both initial treatment groups, showing a population of active CD patients (mean CDAI 293, mean SES-CD 14.6, mean CRP 15.6 mg/L, 41% >10mg/L, oral corticosteroids use 51%, mean daily dose 21.6 mg). A total of 42% of patients were anti-TNF naïve, 58% were anti-TNF non-responder. Most anti-TNF naïve patients (63%) had a disease duration <5 years, whereas 71% of anti-TNF non-responders were diagnosed >5 years. CDAI remission at week 10 was achieved by 47% of filgotinib patients vs. 23% of placebo patients (P=0.0077) [4]. CDAI remission by disease duration is shown in Figure 3.

Figure 3 CDAI remission by disease duration [5]



The percentage of filgotinib-treated patients in clinical remission at week 10 is not impacted by longer disease duration while for placebo-treated patients the percentage of remitters was lower with disease duration of >10 years. In filgotinib-treated patients, consistently high remission rates in both anti-TNF naïve and (to a lesser extent) anti-TNF non-responders were seen, independently of disease duration (anti-TNF naïve: 59%, 60%, 62%; anti-TNF non-responders: 42%, 37%, 32%, for respectively <5 years, 5-10 years and >10 years). Treatment effects of filgotinib were independent of disease location, although a higher percentage of remitters was observed in the subgroup with colonic disease activity only [5].

Serum ustekinumab concentrations positively associated with efficacy

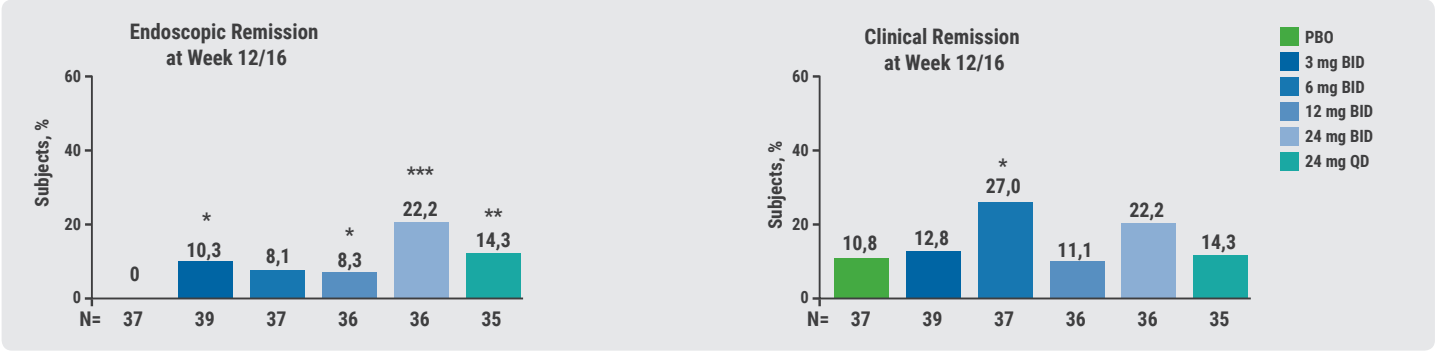
Although subcutaneous ustekinumab maintenance was previously shown to maintain clinical response and remission in moderate-to-severe CD in the phase 3 IM-UNITI maintenance trial, a detailed exposure-response analyses using clinical efficacy, biomarkers of inflammation, and endoscopic sub study data, had not yet been presented. Sandborn et al. presented data based on patients achieving clinical response after a single intravenous dose of ustekinumab in the UNITI-1 and 2 induction studies, who were randomised 1:1:1 in IM-UNITI to subcutaneous placebo, ustekinumab 90 mg q12w, or q8w. Ustekinumab concentration data were categorised into quartiles and endoscopic response relationships were assessed based on week 24 steady-state trough or average steady-state trough values vs. clinical remission, CRP, and endoscopic remission and response (SES-CD <2 or 50% decrease, respectively) in endoscopic sub study patients. The results showed that median steady-state troughs were approximately 3 times greater with q8w subcutaneous ustekinumab (2.11 µg/mL and 0.62 µg/mL for the q8w and q12w regimen, respectively). Ustekinumab levels were lower in patients with higher baseline CRP (likely reflecting greater inflammatory burden), while oral azathioprine, 6-MP, or methotrexate use and weight, did not have any notable effect. Both q8w and q12w were associated with higher proportions achieving clinical remission (e.g. >0.92 µg/mL in q8w quartiles), lower CRP concentrations (in quartiles >1.05 µg/mL), and endoscopic response and remission (in quartiles >0.5 µg/mL) compared to placebo. By receiver operating characteristic analyses, trough concentrations between 0.8 and 1.4µg/mL or greater were associated with greater maintenance of clinical remission. It was concluded that CD patients who received maintenance dosing of ustekinumab 90 mg subcutaneous every 8-12 weeks, serum ustekinumab concentrations were positively associated with efficacy including clinical endoscopic and

biochemical (normalisation of CRP) measures. Steady-state ustekinumab concentrations ranging from 0.8-1.4 g/mL were identified as potential targets for efficacy during maintenance. Although there are assay differences between commercial assays and those in this study, these levels are lower than those reported in the TNF-failure patients in other studies [6]. Unlike anti-TNF agents (e.g. infliximab), ustekinumab levels were comparable between patients receiving and not receiving concomitant immunodulators [7,8]. Another study on ustekinumab evaluated its long-term efficacy and safety and identified predictive factors of ustekinumab failure-free survival in a cohort of anti-TNF refractory CD patients. This was done by a retrospective study in 20 tertiary centres from the GETAID. The primary outcome was ustekinumab failure-free (with failure being defined as withdrawal of ustekinumab due to loss of response, intolerance or need of surgery). Predictive factors of ustekinumab failure-free survival at 24 months, and safety data were also evaluated. Until December 2014, 122 CD patients received subcutaneous ustekinumab induction. A total of 88 patients responded to ustekinumab during the first year and were followed until November 2016. Among these patients (64 females, median age 32.5 years), median disease duration at baseline was 11.8 years; all patients had failed to at least one anti-TNF agent. At time of ustekinumab introduction, 14.8% of patients received immunosuppressant and 14.8% steroids. Median time on ustekinumab was 26.6 months. Ustekinumab failure-free survival (of patients who responded) was observed in 78.4% at 12 months, 65.8% at 24 months and 54.7% at 36 months. Ustekinumab discontinuation was observed for loss of response in 30.6%, for intolerance in 5.6%, for remission in 5.6%, and for pregnancy in one patient; 18.2% of patients underwent intestinal resection during the follow-up. In univariate analysis, concomitant IS at time of ustekinumab introduction and female sex were associated with ustekinumab failure-free survival at 24 months, but not significantly (P=0.07; CI 95% 1.2-24.8) and P=0.05; CI 95% 0.11-1.05), respectively). In multivariate analysis, no predictive factor of ustekinumab failure-free survival was identified. AEs occurred in 22.7% of patients; 1 anal adenocarcinoma was reported during follow-up. This was the first real-life experience of long-term outcome of ustekinumab treatment in patients with refractory CD, with a median follow-up of more than 2 years. More than 50% of patients maintained ustekinumab during the follow-up without loss of response, intolerance or surgery, with a good safety profile. No predictive factor of ustekinumab failure-free survival was identified in multivariate analysis [9].

Upadacitinib effective and safe as induction treatment for refractory CD

In the CELEST study, efficacy and safety of upadacitinib, an oral JAK1 inhibitor, were assessed in patients with moderate-to-severe CD who had inadequate response/intolerance to an immunomodulator or TNF antagonist. Adult patients (18-75 years) with ileal, ileo-colonic or colonic CD for more than 3 months, with a CDAI 220-450, an average daily liquid/soft stool frequency ≥2.5 or daily abdominal pain score ≥2.0, and a Simplified Endoscopic Score for CD (SES-CD) ≥6 (or ≥4 for those with isolated ileal disease), were randomised 1:1:1:1:1:1 to double-blind induction therapy with placebo or upadacitinib at 3, 6, 12, 24 mg twice daily or 24 mg once daily for 16 weeks, followed by a blinded extension therapy for 36 weeks. Patients were also randomised 1:1 at baseline for a follow-up ileocolonoscopy at either week 12/16. From week 2, steroid doses were to be tapered in patients on corticosteroids at baseline. Co-primary endpoints were clinical remission (stool frequency ≤1.5 and abdominal pain ≤1, and both not worse than baseline) at week 16, and endoscopic remission (SES-CD ≤4 and ≥2 point reduction from baseline, no sub-score >1) at week 12/16. Secondary endpoints included a clinical response (≥30% reduction from baseline in abdominal pain or stool frequency with neither worse than baseline), and endoscopic response (≥25% decrease in SES-CD). Of the 220 enrolled

Figure 4 Co-primary endpoints [10]



patients, 82% completed 16 weeks of induction. Mean age was 40.7±12.9 years, CDAI 302.7±63.4 and disease duration 13.2±10.0 years. A total of 69% had failed, or were intolerant to TNF antagonists. Endoscopic remission and clinical remission were achieved by no patients on placebo, whereas 10.3%, 8.1%, 8.3%, 22,2% and 14.3% of patients of upadacitinib 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively. For clinical remission, the percentages were 10.8%, 12.8%, 27.0%, 11.1%, 22.2% and 14.3%, respectively (Figure 4).

A significant dose-response relationship was observed with upadacitinib vs. placebo for endoscopic remission. The secondary endpoint of CDAI remission at week 16 was achieved by 16.2% on placebo, 20.5% on 3 mg BID, 29.7% on 6 mg BID, 38.9% on 12 mg BID, 30.6% on 24 mg BID and 20.0 on 24 mg QD. For a clinical response at week 16, this was 32.4%, 43.6%, 56.8%, 47.2%, 61.1% and 48.6%, respectively. Steroid-free remission at week 16 was achieved by 0%, 20.0%, 22.2%, 38.9%, 33.3% and 10.0%, respectively. AEs occurred more frequently in patients being treated with upadacitinib (Table 6).

Table 6 AE overview [10]

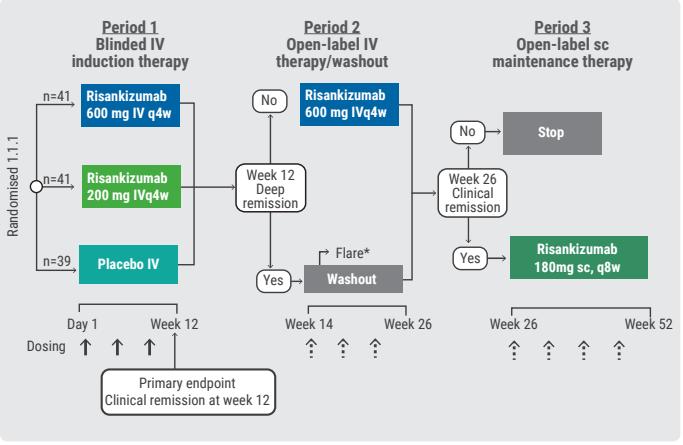
Event, n (%)	Placebo n=37	3 mg BID n=39	6 mg BID n=37	12 mg BID n=36	24 mg BID n=36	24 mg QD n=35
Any adverse event (AE)	27(73)	33 (85)	28 (76)	29 (81)	30 (83)	30 (86)
Any serious AE	2 (5)	5 (13)	2 (5)	10 (28)	3 (8)	7 (20)
Any AE leading to Discontinuation	5 (14)	5 (13)	1 (3)	9 (25)	3 (8)	5 (14)

One case of non-melanoma skin cancer and herpes zoster was reported in the 24 mg BID group, two gastrointestinal perforations were reported, 1 each in the 24 mg BID and 24 mg QD groups. Two adjudicated cardiovascular events (myocardial infarction) were reported in the 12 mg BID group. One death was reported during screening; the patient did not receive study drug. Laboratory abnormalities were mostly ≤grade 2, with 3 events of grade 3 haemoglobin decrease (0 on placebo) and 5 grade 3 creatine phosphokinase elevations (1 on placebo/4 on upadacitinib). It was concluded that upadacitinib demonstrated efficacy and safety as an induction treatment in patients with long-standing and refractory CD [10].

Efficacy of risankizumab for Crohn's disease

The IL-23 pathway has been implicated in the pathogenesis of CD, both genetically and biologically [11,12]. Risankizumab is a humanised monoclonal antibody that inhibits IL-23 through specific targeting of the IL-23 p19 subunit [13]. It was assessed in a randomised phase II study in patients with moderate-to-severe active CD, where it showed to be more effective than placebo for inducing clinical and endoscopic remission at 12 weeks [14]. Re-induction therapy with 600 mg risankizumab increased clinical remission rates further at week 26 and was well tolerated over 26 weeks [15]. The objective of the currently presented maintenance study is to assess efficacy and safety of open-label 180 mg subcutaneous risankizumab maintenance therapy at week 52. The study as a whole was divided into 3 different periods of which period 3 is the study currently presented (Figure 5).

Figure 5 Study design [16]



The outcomes from period 1 and 2 showed that risankizumab was more effective than placebo for inducing clinical and endoscopic remission at 12 weeks, and that re-induction therapy with 600 mg risankizumab increased clinical remission rates further at week 26 and was well tolerated over 26 weeks. At week 26, 51.2% of patients were in clinical remission and entered risankizumab maintenance treatment, with 54 patients completing treatment to week 52. At week 52, 71.0% of patients had clinical remission and 80.6% had clinical response. Of those patients who entered period 3 and had clinical remission at week 12, 87.5% were still in clinical remission at week 52. The rate of endoscopic response and remission at week 52 was 54.8% and 35.5%, respectively. Of those patients who entered Period 3 and had endoscopic remission at week 12, 69.2% were still in endoscopic remission at week 52. Overall, 29.0% of patients were in deep remission at week 52. During Period 3, two patients discontinued due to an AE (worsening and exacerbation of CD). These findings showed that open-label subcutaneous risankizumab was effective as maintenance therapy at week 52 in patients with CD who were in clinical remission at week 26. Subjects randomised to 600 mg risankizumab arm during Period 1 had higher rates of week 52 endoscopic endpoints than those randomised to placebo or 200 mg risankizumab. Overall, risankizumab was well tolerated with no new

safety signals detected during subcutaneous maintenance treatment. The specific blockade of IL-23 via inhibition of p19 warrants further investigation in CD [16].

Vedolizumab resolves extraintestinal manifestations in half of IBD patients

Extraintestinal manifestations (EIM) are common in IBD patients with arthropathies being the most common ones. EIM can also occur upon treatment with anti-TNF agents. Such paradoxical inflammation typically involving the skin is usually considered as a drug class effect and is reversible upon drug cessation. Vedolizumab – a humanised monoclonal antibody that specifically antagonises α4β7 integrin in a gut-specific manner – might be effective on EIM; this was assessed by Tadbiri et al. Between June and December 2014, 173 patients with CD and 121 with ulcerative colitis (UC) were included in the OBSERV-IBD cohort study. Patients were followed up until week 54. Vedolizumab was administered intravenously, 300 mg every 8 weeks through week 54 and every 4 weeks in case of lack of efficacy. EIM such as skin manifestations and arthropathies were assessed at each visit at weeks 0, 6, 14, 22, 30 and 54. Efficacy of vedolizumab on EIM was estimated by using a 3-step scale: (1) complete remission meaning (almost) absence of all clinical symptoms, without increasing the steroid dose or introducing any other IBD-specific treatment, (2) partial response meaning improvement of symptoms or reduction of the steroid dose without worsening of symptoms, (3) no response, meaning no improvement or worsening of symptoms. Among the 294 patients with IBD, 17.2% presented with EIM at baseline including 15.6% with arthropathies and 1.7% with skin manifestations. At week 14, complete remission was observed in 52.2% of patients with arthropathies and in 80% of patients with skin manifestation. At week 54, 45.7% and 60% were still in complete remission for arthropathies and skin manifestations, respectively. During the follow-up period, 15.8% of patients without any EIM at baseline, presented with arthropathies. The probabilities of developing arthropathies during vedolizumab therapy was 5.2%, 10% 13.9% and 17.5% at weeks 14, 22, 30 and 54, respectively. In multivariate analysis, predictors of arthropathies occurrence were prior ankylosing spondylitis (odds ratio (OR)=3.70, CI 95%; 1.49-9.10, P=0.005) and CD (OR=2.50, CI 95%; 1.04-5.88, P=0.04). During the follow-up period, 4.8% of patients presented with paradoxical skin manifestation of whom 57.1% had previously experienced paradoxical skin manifestation associated with anti-TNF therapy. Among the 173 patients with CD, 20.2% presented with active perianal disease at baseline including 17.3% with perianal fistula and 2.9% with perianal fissure. At week 14, complete remission of perianal CD was observed in 42.9% of patients whereas partial remission was observed in 5.7% of patients. At week 54, 34.3% of patients were still in complete remission, whereas 12 discontinued vedolizumab therapy and 13 had no response. Additionally, 3 patients presented with perianal disease during the follow-up period despite vedolizumab therapy. Thus, vedolizumab therapy was effective for achieving complete resolution of EIM in patients with IBD in approximately half of the cases. It was also effective for perianal CD in one third of the patients. Paradoxical skin manifestation may occur upon vedolizumab therapy suggesting a class effect not restricted to anti-TNF agents [17].

TNF blockers might cause histologically proven synovitis in IBD patients

New onset of joint inflammation in patients receiving anti-TNF agents for IBD has been previously described. However, histological characterisation of synovial and bowel compartments has not been reported so far. The aim of the currently presented study was to evaluate the histological characteristics of paired synovial tissue and colonic tissues in IBD patients under TNF blockers. Consecutive IBD patients without history of co-existing joint involvement who developed peripheral arthritis under TNFα blockers, were prospectively enrolled. Each patient underwent rheumatological evaluation and ultrasound assessment (using a Gray scale for synovial hyperthrophy and Power Doppler Signal) of the affected joints. Each patient underwent ultrasound guided synovial tissue biopsy of the knee, following a standardised procedure and colonoscopy with mucosal biopsies [18]. Each synovial tissue and colonic paired sample was stained immunohistochemically for CD68, CD21, CD20, CD3 and CD1172. The results showed that 10 patients with IBD (46.0 years old, 13.2 years of disease duration, 2.5 years of TNF blockers exposure, (CD n=6; UC n=4) were studied. All patients were negative for ACPA, IgM-RF or IgA-RF and 4 patients were under methotrexate therapy. Half of the patients showed endoscopic and histologically proven inflammation of colonic mucosa. Moreover, immunohistochemistry revealed that 60.0% of patients had diffuse and 40.0% had follicular synovitis, respectively. In particular, there was a direct correlation between CD68+, CD21+, CD3+, CD20+ and CD117+ cells distribution in paired synovial tissue and gut tissues in the whole cohort (P<0.05). No significant differences in terms of disease duration (P=0.48), TNFα blockers exposure time (P=0.29), ESR (P=0.26) and CRP (P=0.91) values were found comparing patients with follicular and diffuse synovitis

respectively. These findings suggest that patients with IBD may develop histologically proven synovitis during TNFα treatment, showing similar histological features in terms of CD68+, CD21+, CD20+, CD3+ and CD117+ cells between synovial and colonic compartments. Molecular mechanisms triggered by TNFα blockers leading to joint inflammation have to be clarified [19,20].

Higher anti-TNF serum levels in patients with perianal fistula improve fistula closure

Anti-TNF agents are effective to treat perianal CD and it has been suggested that CD patients with perianal fistulas need higher serum concentrations of infliximab, compared to patients with pure luminal disease in order to attain remission. To evaluate this hypothesis, Strik et al. identified all CD patients with perianal fistula(s) receiving active treatment with infliximab or adalimumab in the Dutch AMC hospital in Amsterdam. Serum drug concentrations of infliximab and adalimumab in CD patients with perianal fistula were collected. Anti-TNF antibody concentrations in patients with a closed fistula, defined by the absence of active draining fistula at physical examination and/or confirmed by MRI, were compared to drug levels in patients with persistently draining perianal fistulas. Only patients receiving anti-TNF maintenance treatment were included and if the time interval between physical examination/imaging and serum drug level measurement did not exceed 4 weeks. Patients who underwent surgical interventions (i.e. a ligation of intersphincteric fistula tract surgery or a faecal diversion procedure) between physical examination/imaging and measurement of anti-TNF serum levels were excluded, as well as patients with internal fistulas. In total, 66 CD patients (out of a total cohort of 352) that received active treatment with infliximab or adalimumab and had perianal fistula(s) were identified. Of those, 71.3% were treated with infliximab and 28.7% with adalimumab. The median serum concentrations of infliximab at trough (interquartile range) were significantly higher in patients with closed fistula(s) (n=32) compared to patients with actively draining fistula (n=15): (6.0 µg/mL (5.4-6.9) vs. 2.3 µg/mL (1.1-4.0), respectively (P<0.001)). The same outcome was seen in 19 patients treated with adalimumab (13 with closed fistula and 6 with active fistula) with a median serum concentration of 7.4 µg/mL (6.5-10.8) vs. 4.8 µg/mL (1.7-6.2) respectively; P=0.003. Receiver operating characteristic analysis of anti-TNF serum measurements showed a high accuracy for both infliximab and adalimumab with an area under the curve of 0.92 (95% CI: 0.82-1.00) and 0.89 (95% CI: 0.71-1.00), respectively. An infliximab serum trough concentration ≥5 µg/mL yielded the optimal results in terms of combined sensitivity of 86.67% (95% CI: 59.5-98.3) and specificity of 84.38 % (95% CI: 67.2-94.7). An adalimumab serum concentration ≥5.9 µg/mL was associated with fistula closure with a sensitivity of 83.3% (95% CI: 35.9-99.6) and specificity of 92.3% (95% CI: 64.0-99.81). There were no differences seen in infliximab and adalimumab dose and intervals between patients with active draining fistula and closed fistula. Thus, an association was found between the level of anti-TNF serum concentrations and fistula closure in CD patients. Pursuing higher serum anti-TNF serum levels in CD patients with perianal fistula might improve fistula closure rates [21].

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Microbiome and Microbiota

Recognition of the crucial role of the microbiome and microbiota in gastrointestinal diseases is increasing, with faecal microbiota transplantation (FMT) now established as a therapeutic option for various gastrointestinal disorders. Enriching the microbiome with multispecies probiotics seems a promising strategy.

Single faecal infusion not effective in patients with severe CDI

FMT has shown to be an effective therapeutic option against recurrent Clostridium difficile infection (rCDI) [1]. A growing body of evidence shows that a single faecal infusion achieves lower CDI cure rates than multiple faecal infusions [2-3]. This finding is particularly remarkable when dealing with severe CDI, which has been identified as a predictor of failure after single faecal infusion [4-5]. However, to date the efficacy outcomes of single and multiple faecal infusions for the treatment of severe CDI have been compared only in few studies [2]. Ianiro et al. evaluated a prospective cohort of patients who received FMT by colonoscopy for severe rCDI from June 2013 to January 2017. Severe CDI was defined as an episode of CDI with one or more specific signs and symptoms of severe colitis, or a complicated course of disease, with significant systemic toxin effects and shock, and consequent need for Intensive Care Unit (ICU) admission or colectomy [6]. Treatment failure was defined as post-procedural persistence of diarrhoea, or diarrhoea recurrence after early improvement within 8 weeks after faecal infusion. Clinical cure was defined as disappearance of diarrhoea. Multiple faecal infusions were administered when a single faecal infusion failed to treat CDI. Selection of donors, preparation of fresh and frozen faeces, and FMT procedure, were carried out as previously reported [2,7]. All patients were carefully followed up until 8 weeks after FMT, by weekly clinical examinations. During the study period, 33 subjects with severe rCDI received FMT. The majority of patients was female (n=20) and the average age was 74 years (range 60-93). The mean number of previous recurrences was 3 (range 1-5). Pseudomembranous colitis was identified at endoscopic evaluation in 67%. A single faecal infusion was able to cure 27%; among non-responders to single faecal infusions, 3 critically-ill subjects were not able to repeat the procedure; 2 of them died of overwhelming CDI, and the other subject died of other reasons which were not related to CDI. All remaining 21 subjects received repeated faecal infusions (mean=3; range 2-5), and 90% were successfully treated. In this series of patients, a total of 68 infusions of faeces was performed, using faeces from unrelated donors in 69% and frozen faeces in 40%. Overall, FMT (including single and multiple infusions) was able to cure 85% patients with severe CDI. These findings remark that single faecal infusion is not effective in patients with severe CDI, and should be no longer considered as a reliable treatment options for this clinical picture. As severe CDI is a life-threatening disease, dedicated protocols, including multiple-infusion FMT, are necessary to offer patients an effective therapeutic option to cure this condition [8].

Beneficial effect FMT on symptom scores and quality of life in IBS patients

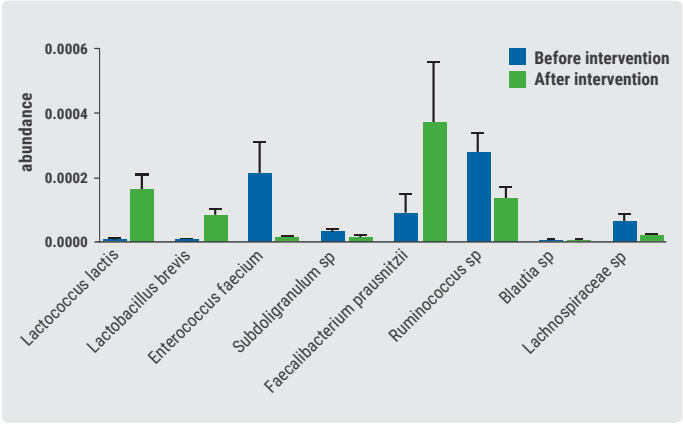
Due to the potential involvement of the gut-brain-axis in the pathogenesis of IBS and the reported altered gut microbiota composition in IBS patients, FMT is suggested as a potential effective treatment in IBS patients [9]. So far, no placebo-controlled randomised clinical trials have been reported. The aim of the study by Holster was to investigate the effect of FMT on the symptoms of IBS patients in a randomised, double-blinded placebo-controlled trial. A total of 16 IBS patients were included; 8 patients received donor faeces material (treatment) and 8 received their own faeces material (placebo) via colonoscopy into the caecum. Symptom scores were assessed by the IBS - Symptom Severity Score (IBS-SSS) and Gastrointestinal Symptom Rating Scale - IBS (GSRS-IBS) before and at several time points after intervention. QoL was assessed by IBS-QoL and SF-36 before and after intervention. Anxiety and depression symptoms were assessed by the Hospital Anxiety and Depression scale (HADS). Differences in questionnaire scores from baseline as well as between treatment and placebo were assessed with one- and two-sample t-tests, respectively. The IBS-SSS scores of patients receiving donor faecal material significantly decreased 4 weeks and 8 weeks after FMT compared to baseline (mean difference: -61.6±50.8, $P<0.01$, and -63.3±43.1, $P<0.01$, respectively). No significant differences in the placebo group compared to baseline were observed, and neither between treatment and placebo. The GSRS-IBS total score significantly decreased for

both the treatment and the placebo group 2 weeks after FMT (-0.46±0.32 P<0.01, and -0.71±0.73 P<0.05, respectively) and 4 weeks after FMT compared to baseline (-0.79±0.57, P<0.01, and -0.57±0.63, P<0.05, respectively). Again, no differences between the two intervention groups were observed. The IBS-QoL total score was significantly increased in the treatment but not in the placebo group at 8 weeks (10.0±6.3, P<0.01). Similar results were observed in three out of eight SF-36 sub-scores, especially in the general health sub-score. This score was significantly increased in the treatment group compared to the placebo group 8 weeks after FMT (11.8±8.3 compared to -8.1±11.3, P<0.01). No significant differences were observed in the HADS scores, however, in the treatment group, the depression sub-scores showed a trend towards reduction 8 weeks after FMT compared to baseline (-1.4±0.9, P=0.08). This trend did not occur in the placebo group. These data showed that there is a beneficial effect of FMT on symptom scores and QoL in IBS patients. This effect is also observed in the placebo group, although to a lesser extent, indicating that placebo-controlled studies are essential in IBS patients. It was noted that the bowel cleansing and the processing of the autologous faecal material might have contributed to the placebo effect. Further analysis on individual basis, separation into non-responders and responders as well as correlation with additional outcomes such as microbiota composition will provide more insight [10].

Microbiome enrichment with probiotics in cirrhotic patients

Cirrhosis is accompanied by significant changes of the intestinal microbiome including the overgrowth of the intestine with potential pathogens that can translocate through a weakened gut barrier and cause severe infections. Horvath et al. hypothesised that probiotic bacteria repress intestinal pathogen growth and strengthen the gut barrier. To test this hypothesis, a randomised, double-blind, placebo-controlled study was performed to test the effects of the multispecies probiotics. A daily dose of 6 g probiotics (n=26) or placebo (n=32) was administered to 58 patients with Child's A cirrhosis during 6 months, followed by a 6 months observation period. The probiotic contained 1.5*1010 CFU of Bifidobacterium bifidum W23, Bidifobacterium lactis W52, *Lactobacillus* brevis W63, *Lactobacillus acidophilus* W37, *Lactobacillus salivarius* W24, *Lactobacillus casei* W56, *Lactococcus lactis* W19, and *Lactococcus lactis* W58. Stool microbiome was analysed prior, immediately after the intervention and six months following the end of treatment. Machine-learning algorithms identified 37 operational taxonomic units that best characterise microbiome changes by the probiotic (Figure 6).

Figure 6 The most discriminative operational taxonomic units [11]



Lactobacillus brevis and *Lactococcus lactis* were significantly increased after six months of intervention while *Enterococcus* was mainly present in patients with proton pump inhibitors. Its abundance was significantly reduced after six months of intervention and stayed low after the end of treatment.

It was concluded that after a six-month intervention with probiotics, an increase in probiotic bacteria and a decrease of *Enterococcus* in stool of cirrhotic patients was evident. However, the colonisation with probiotics was not permanent and ongoing administration might be necessary to achieve long-term effects.

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Pancreatitis

As pancreatitis is a complicated condition with a high risk of adverse outcomes, predicting incidence as well as disease progression is very important. New findings indicate that certain factors such as emergency ECRP and p21 play a key role.

PEP incidence lower in emergency ERCP compared to elective ERCP

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is a potentially serious complication, and some risk factors for PEP have been reported in general ERCP in previous studies. Emergency ERCP is different from normal state ERCP, and the risk factors for PEP in emergency ERCP are not clear. Nakai et al. aimed to identify the incidence and risk factors for PEP in emergency ERCP. A prospective study (consisting of two sub studies) of 2,078 cases undergoing diagnostic and therapeutic ERCP at five Japanese institutions, was performed between April 2015 and May 2016. The exclusion criteria were active pancreatitis, choledochojejunostomy, inability to approach a papilla, and inspection aimed at only the pancreatic duct. Emergency ERCP was defined as unscheduled inspections performed within and outside duty hours. The definition of PEP was met when two of the following three conditions were met: (1) serum amylase level more than three times the upper limit of the normal range in each institution, (2) continuous abdominal pain for over 24 hours, and (3) presence of pancreatitis findings on computed tomography. The first substudy involved comparison of the incidence of PEP and its characteristics between emergency and elective ERCP, whereas the second sub study involved determining the predictive risk factors for PEP in emergency ERCP using univariate and multivariate analyses. A total of 1,677 cases (elective ERCP n=1,248, emergency ERCP n=429) was analysed in this study. The results of the first sub study showed that PEP developed in 4.7% from the emergency group and in 8.1% from the elective group; thus, the incidence of PEP was significantly lower in the emergency group than in the elective group (OR=0.58, 95% CI: 0.33–0.95, P=0.03). Endoscopic sphincterotomy, stone removal, papillary balloon dilatation, and intraductal ultrasound sonography were performed significantly more often in the elective group than in the emergency group (P<0.001). Placement of a biliary stent was significantly more common in the emergency group than in the elective group (88.3% vs 56.3%). In addition, the procedure time was significantly longer (P<0.001) and the number of endoscopists who had more than five years of experience was significantly higher (P=0.04) in the elective group than in the emergency group. Univariate analysis of the second sub study (n=248) showed that contrast injection into the pancreatic duct, more than four cannulation attempts increased and placement of a biliary stent decreased the risk of PEP in emergency ERCP. Multivariate analysis showed that contrast injection into the pancreatic duct (OR=4.51, 95%CI: 1.64–12.40, P=0.0035) increased the risk of PEP in emergency ERCP (Table 7).

Table 7 Predictive risk factors for PEP in emergency ECRP with naïve papilla [1]

	PEP (+) n=20	PEP (-) n=20	Univariate *P*-value	Multivariate OR (95%CI)	Multivariate *P*-value
Median age, year, (SD)	75.5 (37-93)	79 (21-100)	0.17	–	–
Gender Male Female	8 (40.0) 12 (60.0)	137 (60.1) 91 (39.9)	0.9	0.51 (0.20-1.34)	0.17
History of previous pancreatitis, n(%)	1 (5.0)	39 (3.9)	0.82	–	–
Serum bilirubin, n(%) <2mg/dL	9 (45.0)	64 (28.1)	0.12	–	–
Aetiology, n(%) Benign Malinancy	17 (85.0) 3 (15.0)	173 (75.9) 55 (24.1)	0.36	–	–
Juxtapapillary diverticulum, n(%)	7 (35.0)	83 (36.4)	0.90	–	––
Experience of the operator, n(%) <5year	16 (80.0)	169 (74.1)	0.56	–	–
Average procedure time, min., (SD)	31.9 (5-139)	37.4 (12-68)	0.25	–	–
Contrast injection into PD, n(%)	**12 (60.0)**	**60 (26.3)**	**0.0028**	**4.51 (1.64-12.40)**	**0.0035**
More than 4 cannulation attempts, n(%)	**15 (75.0)**	**117 (51.3)**	**<0.05**	**1.91 (0.64-5.77)**	**0.25**
Guide wire insertion into PD, n(%)	5 (25.0)	47 (20.6)	0.65		
Catheter insertion into PD, n(%)	**10 (50.0)**	**61 (26.8)**	**0.03**	**0.37 (0.06-2.26)**	**0.28**
Pre-cut, n(%)	1 (5.0)	3 (1.3)	0.24	3.38 (0.25-45.8)	0.36
Endoscopic sphincterotomy, n(%)	7 (35.0)	64 (28.1)	0.51	–	–
Balloon dilatation, n(%)	1 (5.0)	4 (1.8)	0.34	–	–
Placement of EBS, n(%)	**14 (70.0)**	**201 (88.2)**	**0.028**	**0.70 (0.16-3.03)**	**0.63**
Placement of Pancreatic duct stent, n(%)	1 (5.0)	17 (7.5)	0.69	–	–
Intraductal ultrasound, n(%)	2 (10.0)	18 (7.9)	0.74	–	–
Stone removal, n(%)	5 (25.0)	29 (12.7)	0.13	–	–

It was concluded that the incidence of PEP was lower in emergency ERCP than in elective ERCP, and it was largely unaffected by the endoscopists' experience and the procedure time. This may be associated with a tendency to avoid invasive procedures in emergency cases, and it is considered that only placement of a biliary stent contributes to a decrease in the development of PEP. Close attention should be paid for contrast injection into the pancreatic duct, particularly when attempt of cannulation for naïve papilla are required [1].

Coronary disease and CODP no predictors of worse outcome in acute pancreatitis

Carvalho et al. evaluated the effect of chronic ischemic heart disease and chronic obstructive pulmonary disease (COPD) in the outcome of acute pancreatitis (AP) [2]. This was one by a retrospective cohort study including all patients admitted with AP from January 2003 to December 2016, in a tertiary referral centre in Portugal. Demographic and clinical variables were analysed by logistic regression (SPSS v23). Clinical outcomes included organ failure, persistent organ failure (>48h), intensive care unit admission and mortality. A total of 553 patients with AP were included of which 58.4% was male and a median age of 80 (18-98) years. Most common aetiologies included gallstones (38.9%) and alcohol (27.3%). A total of 23% developed organ failure (in 43% persistent) and 26.8% were admitted in UCI. Mortality rate was 5.6% (n=31). A total of 10.1% had previous history of coronary disease and 5.1% had been diagnosed with COPD. The presence of coronary disease and Chronic Obstructive Pulmonary Disease (CODP) were not associated with higher ranson's score (≥3), P=0.076 and P=0.959, respectively. No association was found between previous history of coronary disease and the development of organ failure (P=0.525), persistent organ failure (P=0.287), need for ICU admission (P=0.115) and mortality (P=0.262). There was also no association found between previous history of CODP and the development of organ failure (P=0.803), persistent organ failure (P=0.588), need for ICU admission (P=0.514) and mortality (P=0.720). At multivariate analysis (correcting for age and gender) coronary disease and CODP were not independent predictors of worse outcome in AP. Thus in this population, a previous history of coronary disease and CODP were not predictors of worse outcome in AP.

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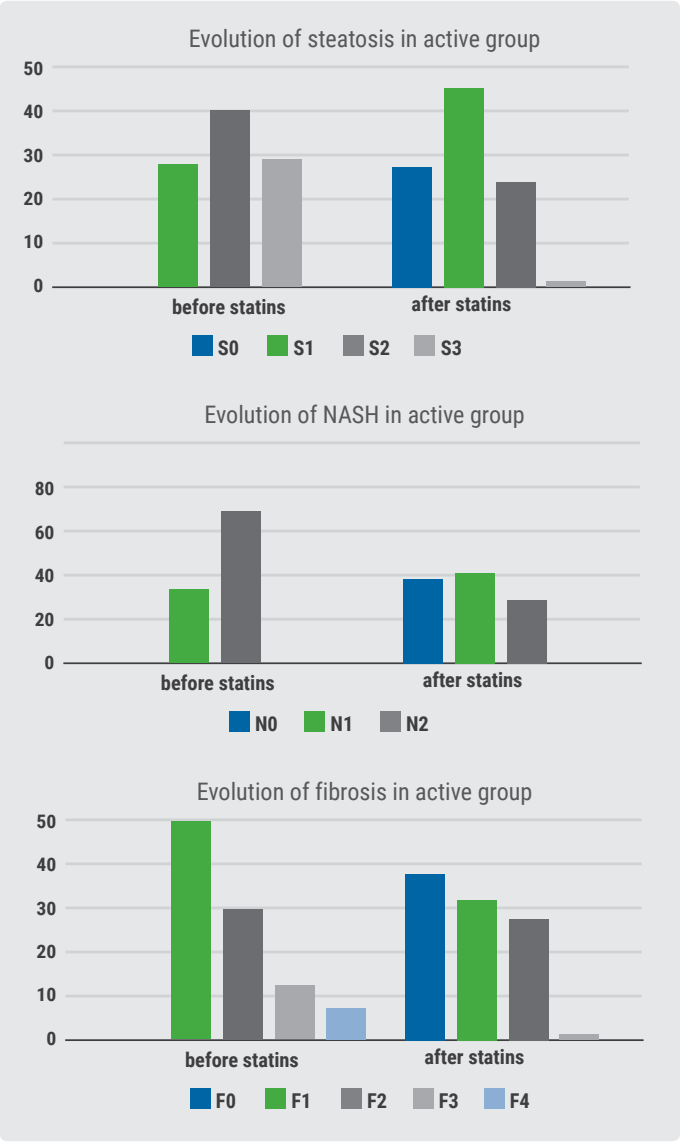
NASH/NAFLD

There is a growing interest in unravelling the patterns of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), which is reflected by the wide scope of research. Underlying genetic and physiological factors can be used as predictors of disease and the potential role of drugs such as statins seems promising.

Possible favourable effects statins on liver fibrosis

NASH is considered an important risk factor for liver fibrosis. Although literature data indicates that statins may be beneficial when given for NASH treatment, recent reports are controversial [1]. To evaluate if statins independently influence the evolution of fibrosis accompanying NASH using FibroMax, 120 patients with NASH and metabolic syndrome were followed-up for a period of 3 years. Patients taking a series of drugs, with genetic metabolic disorders or impaired intestinal absorption (celiac disease) or alcoholics were excluded. Steatosis, fibrosis and NASH were quantified by using the FibroMax scales at baseline and after three years of statin treatment. Patients were randomised in two groups: the active group of 60 patients receiving low-dose hydrophilic statin (rosuvastatin 5 mg/day) and the witness group of 60 patients, matched by age, gender and sex, receiving placebo. The follow-up period was fulfilled by 97% of subjects. The FibroMax staging at baseline showed the following results in the active group: S1 29%, S2 41% and S3 30%; F1 50%, F2 30%, F3 13% and F4 7% of patients, respectively N1 31% and N2 69%. The staging according to FibroTest, SteatoTest and NashTest was similar in the placebo group. After 3 years of low-dose hydrophilic statin, the mean alanine aminotransferase (ALT) level from active group decreased from 72.22 IU/L to 32.80 IU/L (P<0.05); in the witness group no significant ALT decrease was noticed (69.34 IU/L to 58.17 IU/L, P>0.5). The FibroMax showed an important improvement of steatosis and fibrosis in the active group, compared with the witness group. After three years of statins, the active group was stratified as follows: S0 27%, S1 46%, S2 25%, respectively S3 2% of patients, respectively F0 38%, F1 32%, F2 28%, F3 2%; F4 0% of patients. NashTest also proved a positive evolution under statin treatment, compared with placebo (N0 36%, N1 40% respectively N2 26%, P>0.001).

Figure 7 Various outcomes before and after statin use [2]



After adjusting for age, body mass index (BMI) diabetes, low density lipoprotein (LDL)-cholesterol and triglyceride levels, statin therapy showed a significant correlation with steatosis, fibrosis and NASH stages improvement in the active group (r=0.92, r=0.87, respectively r=0.95, P<0.005) [2].

Genetic factors important in non-obese NASH patients

Genetic factors seem to be more important in non-obese NASH patients as was shown by a study in which TT genotype of methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism was more frequent, especially in non-obese NASH patients than in healthy controls. It is thought that MTHFR A1298C and C677T gene polymorphisms contribute to aetiopathogenesis of NASH due to their effects in homocysteine metabolism. Ates et al. aimed to determine the relationship between the NASH and MTHFR C677T and A1298C gene polymorphisms, especially in non-obese NASH patients [3]. A total of 88 NASH patients (52 males/36 females with a mean age of 45 years), and 90 healthy controls (53 males/37 females with a mean age of 41 years) were included in the study. MTHFR A1298C and C677T gene polymorphisms were investigated and the NASH patients and controls were compared. NASH patients were assigned to two groups according to whether they were obese. According to BMI values of NASH patients, 55 patients were non-obese and 33 patients were obese. There was no statistically significant difference between distribution of MTHFR A1298C polymorphism of NASH patients and controls (P>0.05). The proportion of proportion of TT genotype of MTHFR C677T polymorphism of NASH patients was significantly higher than that of controls (P<0.01). This was also the case in in non-obese NASH patients (P<0.01). However, the proportion of TT genotype of MTHFR C677T polymorphism of obese NASH patients was not significantly different than that of the control group (P>0.05). MTHFR C677T CC (wild) genotype was significantly lower in non-obese NASH patients than controls (P<0.05).

Table 8 Comparison of MTHFR A1298C and C677T gene polymorphism genotype frequencies between obese and non-obese NASH patients and healthy control group

MTHFR		Obese NASH (n=33)	Healthy Control (n=90)	Odds ratio (95% CI)	P
A1298C	CC	3 (9%)	20 (22%)	0.295 (0.035 - 2.484)	0.261
	AC	25 (76%)	50 (56%)	3.011 (0.752 - 12.060)	0.119
	AA	5 (15%)	20 (22%)	0.533 (0.106 - 2.686)	0.446
C677T	TT	4 (12%)	3 (3%)	5.091 (0.646 - 40.097)	0.122
	CT	12 (36%)	33 (37%)	1.101 (0319 - 3.802)	0.879
	CC	17 (52%)	54 (60%)	0.563 (0.168 - 1.890)	0.343

MTHFR		Non-Obese NASH (n=55)	Healthy Control (n=90)	Odds ratio (95% CI)	P
A1298C	CC	12 (22%)	20 (22%)	1.011 (0.337 - 3.026)	0.984
	AC	25 (45%)	47 (52%)	0.621(0.247 - 1.562)	0.311
	AA	18 (33%)	23 (26%)	1.725 (0.650 - 4.581)	0.273
C677T	TT	15 (27%)	3 (3%)	9.975 (1.911- 52.04)	**0.008**
	CT	12 (44%)	33 (37%)	1.448 (0.573 - 3.660)	0.434
	CC	6 (29%)	54 (60%)	0.289 (0.109 - 0.766)	**0.012**

Patients with renal failure and low vitamin D have high risk of NAFLD/NASH

Although it has been suggested that an association exists between low vitamin D levels with NAFLD and NASH, as well as metabolic syndrome and diabetes mellitus, causality could not yet be proven. Gehring et al. sought to identify patients who have a higher risk of developing NAFLD/NASH

in a selected patient cohort being admitted to the department of nephrology of the University Hospital Marburg for renal disorders [4]. A total of 176 patients whose plasma vitamin D concentration, phosphate and parathormone levels and liver enzyme levels had been quantified beforehand, were enrolled. A retrospective investigation of laboratory parameters (including electrolytes, hormones, and vitamins) and pre-existing medical conditions (including high blood pressure, diabetes mellitus, hyperlipoproteinaemia) followed. Patients were divided into 4 groups according to plasma vitamin D levels (normal >25 ng/mL; low <25 ng/mL) and transaminase levels (aspartate aminotransferase (AST)/ALT/γ-GT >30 U/L; normal: AST/ALT/γ-GT <30 U/L). Low 1,25-hydroxyvitamin D levels correlated significantly with high creatinine, urea, and LDL levels, while low 25-hydroxyvitamin D levels correlated with high cholesterol and trigylceride levels, suggesting a relationship between low vitamin D levels and fat metabolism disorders. Interestingly, end stage renal failure (chronic haemodialysis) was significantly correlated with the development of NAFLD/NASH with significantly higher levels of AST/ALT and gGT, hyperparathyroidism and hyperphosphataemia. Moreover, transaminases were significantly lower if vitamin D was supplemented. It was concluded that vitamin D deficiency is often present in patients with kidney diseases such as chronic renal failure and that vitamin D levels are correlated to age and sex of the patient. Patients suffering from renal failure have a high risk developing NAFLD/NASH if they have diminished vitamin D levels and supplementing vitamin D offers protection from NAFLD/NASH. The correlation of hyperparathyroidism and NAFLD/NASH has now to be further investigated in larger patient groups.

High body fat level only predictor of NAFLD

Bakulin et al. studied the prevalence of steatosis according to elastometry with controlled attenuation parameter among young people and associated specific body composition [5]. A total of 59 volunteers (all were medical students) between the ages of 19-28 years (median age 20.5 years) participated in this research. The majority was female (62.7%) without verified liver diseases. The survey was conducted in order to exclude or detect risk factors. Determining the presence and degree of steatosis and the stage of liver fibrosis was performed with FibroScan 502 Touch; the final figures of elasticity of the liver were estimated in kPa. The controlled attenuation parameter in dB/m was used for the severity of steatosis. Moreover, the Bioelectrical Impedance Analysis (BIA) of the body was evaluated (BMI, body fat). The results showed signs of liver fibrosis and steatosis in 25.4%. The signs of steatosis were founded in 20.3% of students (CAP>215 dB/m), and liver fibrosis in 11.9% (E>5.8 kPa). At the same time, the combination of liver fibrosis and steatosis was diagnosed in 6.8%. After analysing data of BIA, it was revealed that 40.3% of cases was overweight and 33.4% was obese. Results of binary regression analysis showed that the only predictor of NAFLD was high body fat level. Transient elastography with controlled attenuation parameter is a fast, repeatable non-invasive method for the early diagnostics of NAFLD. The importance of assessing BIA is confirmed but the importance of using BMI to assess NAFLD development has not been proven. According to the results of BIA, the development of liver steatosis is strongly associated with high body fat level.

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Oncology

Gastro-intestinal oncology has seen some exciting therapeutic advances in recent years, such as immunotherapy. Nevertheless, prevention and timely diagnosis remain important.

Higher cancer incidence after DAA

The incidence of liver cancer and its recurrence have been reported frequently at an early stage in patients who underwent interferon-γ -free direct-acting antiviral (DAA) therapy for chronic hepatitis C (HCV) [1,2]. The underlying mechanisms of cancer incidence following DAA therapy may include the rapid clearance of HCV, reconstitution of the immune system, and reduction of cancer immunosurveillance. These changes may in fact have an impact on the development of cancer in other organs. Endoh et al. aimed to evaluate the early occurrence of non-liver cancer following DAA therapy in

a retrospective, single-centre, cohort study. The hypothesis was that non-liver cancer incidence in patients with sustained virologic response (SVR) following interferon-γ -free DAA therapy (DAA group) will be significantly higher than in patients with SVR following interferon-γ -based therapy. Patients eligible for inclusion were those who had initiated antiviral therapy and who achieved SVR12. Patient records were examined to identify new cases of non-liver cancer, as diagnosed through pathological examination. The study cohort consisted of patients treated with interferon-γ -free DAA therapy (n=390, of which 13 did not achieve SVR and 14 were drop-outs) and patients treated by interferon-γ -based therapy (n=681 of which 206 did not achieve SVR and 28 were drop-outs). It was found that there were 16 and 23 cases of cancer occurring in organs other than the liver in the DAA and interferon-γ groups, respectively. The independent risk factors for non-liver cancer occurrence were DAA therapy, former of current smoking, and high FIB-4 index (Table 9).

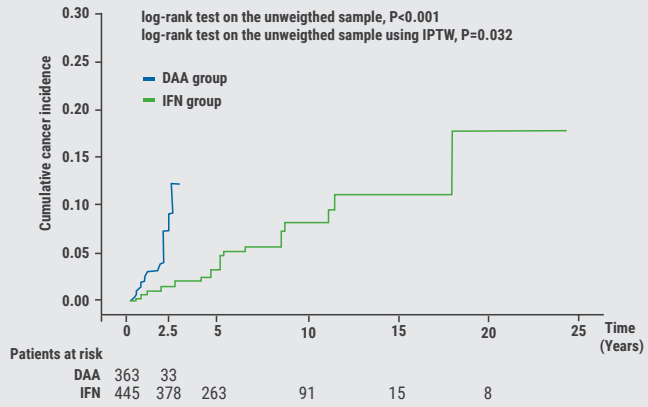
Table 9 Factors associated with non-liver cancer occurrence in Cox regression analyses [3]

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
DAA group (ref. IFN group)	**10.02 (3.74-34.36)**	**<0.001**	**6.70 (2.46-18.24)**	**<0.001**
Age > 65 years	**4.00 (1.94-8.24)**	**<0.001**		
Sex (male)	1.48 (0.79-2.98)	0.280		
Body mass index >23kg/m^2	0.94 (0.48-1.85)	0.867		
Former or current smoking	1.48 (0.77-2.87)	0.244	**2.04 (1.09-4.13)**	**0.037**
Habitual alcohol intake	0.75 (0.33-1.71)	0.495		
History of IFN therapy	0.92 (0.35-2.42)	0.869		
AST >1.5 x ULN	1.03 (0.52-2.02)	0.932		
ALT >1.5 x ULN	0.94 (0.47-1.85)	0.846		
Albumin > 4 g/dL	**0.41 (0.21-0.82)**	**0.012**		
Bilirubin > 0.8 mg/dL	1.48 (0.73-2.98)	0.278		
Haemaglobin > 13.5 g/dL	**0.47 (0.23-0.96)**	**0.038**		
Platelet count > 15 x 10^4/µL	**0.40 (0.19-0.81)**	**0.011**		
AFP > 5 ng/mL	0.68 (0.34-1.35)	0.265		
eGFR > 60 mL/min/1.73m^3	0.30 (0.14-0.63)	0.002		
Diabetes Mellitus	0.98 (0.41-2.37)	0.966		
History of HCC	**2.26 (1.02-5.03)**	**0.045**		
History of non-liver cancer	1.02 (0.24-4.27)	0.978		
Fibrosis-4 index >3.25	**2.32 (1.20-4.54)**	**0.012**	**2.13 (1.09-4.13)**	**0.026**
Child-Pugh Score > 5	1.36 (0.48-3.87)	0.566		

HCC = hepatocellular carcinoma; AFP = Alpha-fetoprotein; eGFR = estimated Glomerular filtration rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase

After correcting for possible confounding factors including age, sex, cigarette smoking, habitual alcohol intake and other covariables, the difference in incidence of non-liver cancer was significant based on the Kaplan-Meier estimation (P=0.032) and the Cox regression analysis (P=0.005) (Figure 8).

Figure 8 Cumulative cancer incidence by Kaplan-Meier curves [3]



Researchers noted that because cancer detection in organs other than the liver can be challenging in the management of hepatitis, some cases with cancer found after the treatment might have been diagnosable before the treatment. Possibly, this could have led to an overestimation of the incidence after the treatment. The number of newly diagnosed cancer cases was small in the present study, resulting in a low statistical power. Nevertheless, the cancer incidence in organs other than the liver was significantly higher in patients treated with DAA therapy than those treated with interferon-γ therapy. This difference persisted after correcting for possible confounding factors. It was finally concluded that patients must be more carefully examined for the early occurrence or development of cancer in organs including, but not limited to, the liver, after the initiation of DAA therapy than those of interferon-γ therapy [3].

FIT over gFOBT preferred as CRC screening stool test

Worldwide, many colorectal cancer (CRC) screening programs use non-invasive faecal occult blood tests (FOBTs). Although the interval CRC (iCRC) rate is an important performance indicator of a screening program, data on iCRC after negative FOBTs are limited. A Dutch review and meta-analysis compared the pooled incidence of guaiac faecal occult blood test (gFOBT) iCRCs and faecal immunochemical test (FIT) iCRCs in population-based CRC screening programs. Also, the ratio of screen-detected vs. FOBT iCRCs was assessed. Ovid Medline, Embase, The Cochrane Library, the Science Citation Index, PubMed publisher and Google scholar were searched up to May, 2016. All studies reporting on the incidence of FIT or gFOBT iCRCs in average CRC screening populations were included. The main outcome was pooled incidence rate of iCRCs per 100,000 person-years. FOBT iCRC was defined as cancer which developed after a negative FOBT and before the next FOBT was due. A total of 5.882 records

were identified, of which 413 full-text articles were assessed for eligibility and 30 studies were included in both qualitative and quantitative syntheses. Meta-analyses comprised data of 7,196,939 screening participants with negative FIT in which 13,922 screen-detected CRCs and 5,240 FOBT iCRCs were documented. Pooled incidence rates of iCRC following FIT and gFOBT were 20 (95%CI 14-28; I2=94%) and 40 (95%CI 26-61; I2=93%) per 100,000 person-years, respectively. The pooled incidence rate ratio of FIT iCRC compared to gFOBT iCRC was 0.47 (95%CI 0.24-0.95). For every FIT iCRC, 3 CRCs were found with FIT, while for gFOBT the ratio between iCRC and screen-detected CRC was 1:1.3. No significant differences were found between the relative risk of FOBT iCRC in the second and third screening round compared to the first, with 1.03 (95%CI 0.94-1.13) and 1.08 (95%CI 0.93-1.22), respectively. The incidence rate ratio of FOBT iCRC was 1.2 (95%CI 0.8-1.7) for males relative to females and 5.0 (95%CI 1.2-21) for screened patients aged ≥60 relative to <60 years. This was the first study to report on the pooled incidence of FIT and gFOBT iCRC in screening setting and the incidence rate of iCRC after a negative FOBT is two-fold higher in gFOBT than in FIT, which supports the use of FIT over gFOBT as screening stool test. However, for every three FIT-detected CRCs, still one CRC is missed, which highlights the importance to adequately inform screened patients about the risk of developing a colorectal carcinoma after a negative FIT [4].

Increased risk of HCC after HCV clearance

Dr. Reig and colleagues addressed whether (treated) HCV patients have an increased risk of hepatocellular carcinoma (HCC). She identified three groups: de *novo* patients without history of HCC, patients with recurrent HCC and patients who received a liver transplant (recurrence of drop-out while on waiting list due to HCC). Recent results from a study by Carret et al. in de *novo* patients showed that the HCC risk was up to 1.66 higher than interferon-γ therapy (hazard ratio adjusted for DAA 1.19 [0.85-1.66, P=0.3178]) [5]. Therefore, the de *novo* incidence in cirrhotic HCV-DAA treated patients seems to be higher within the 1st year than what is expected. However, better characterisation of patients prior to treatment is needed to understand the real impact of DAA on the development of HCC. The same is true for HCV-DAA treated patients who had had resection, percutaneous treatment and/or transarterial chemoembolisation), the incidence of HCC also seems higher in the 1st year. Currently, very little evidence is available with regard to the impact of HCC recurrence after liver transplantation in HCV-DAA treated patients. More research is therefore needed to elucidate the remaining uncertainties [6].

Immunotherapy in cancer treatment

Immunotherapy has been a real 'game changer' since its introduction in cancer treatment. Successes that have been observed with this type of treatment have been achieved with checkpoint inhibitors, such as the programmed death (PD)-antibodies and CTL4 –antibodies. Pembrolizumab and nivolumab have demonstrated durable responses in those patients exhibiting a response [7,8]. Of patients (n=39) with recurrent or metastatic PD-L1-positive gastric cancer who were treated with pembrolizumab, 22% showed overall response (partial), with a manageable toxicity profile [9]. A recent randomised, double-blind, placebo-controlled, phase 3 trial in 493 Asian patients with non-resectable advanced or recurrent gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, standard therapy (including two or more previous chemotherapy regimens) were treated with nivolumab or placebo. At the data cut-off, median follow-up in surviving patients was 8.87 months for the nivolumab patients and 8.59 months for the placebo group. The survival benefits indicate that nivolumab might be a new treatment option for heavily pre-treated patients with advanced gastric or gastro-oesophageal junction cancer (Table 10) [10].

Table 10 Outcomes non-resectable advanced/recurrent gastric/refractory gastro-oesophageal junction cancer [10]

	Nivolumab	Placebo
Median OS	5.26 months (95% CI 4.60-6.37)	4.14 months (3.42-4.86)
12-month overall survival	26.2% months (95% CI 20.7-32.0)	10.9% months (6.2-17.0)

Furthermore, a global, multicohort, phase 2 study of pembrolizumab in 259 patients with advanced gastric or gastro-oesophageal junction cancer showed promising results with manageable safety after ≥2 prior lines of therapy. The overall objective response rate (complete response + partial response) was 11.2%; 1.9% of patients had a complete response, 9.3% had a partial response. A total of 17% had stable disease, and 55.6% (95% CI, 49.3-61.7) had progressive disease [11]. Currently, a wide variety of ongoing phase 3 trials – such as KEYNOTE-061/-062, CHECKMATE-649, ONO-4538-37 and JAVELIN300 – is assessing the effects of pembrolizumab, avelumab and nivolumab. All trials evaluate the optimal timing, the impact of PD-L1 and combination therapy with chemotherapy [12].

For advanced HCC, the only worldwide approved drug at the moment is sorafenib. However, research for newer, better treatment options has also shifted to immunotherapeutic agents. El-Khoueiry et al. assessed safety and efficacy of nivolumab in a phase 1/2, open-label, non-comparative, dose escalation and expansion trial (CHECKMATE-040). Patients

were allowed to have used sorafenib prior to enrolment. Patients (n=262) received intravenous nivolumab 0.1-10 mg/kg every 2 weeks in the dose-escalation phase (3+3 design). Nivolumab 3 mg/kg was given every 2 weeks in the dose-expansion phase to patients in four cohorts: sorafenib untreated or intolerant without viral hepatitis, sorafenib progressor without viral hepatitis, HCV infected, and hepatitis B virus infected. At the time of interim analysis,

77% of patients had completed treatment and follow-up is currently ongoing. The overall response rate was 20% (95% CI 15-26) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI 6-28) in the dose-escalation phase. The median OS in sorafenib naïve patients was 28.6% vs. 15.6% in sorafenib-experienced patients. The safety profile of nivolumab was manageable and no new signals were observed in patients with advanced HCC. Durable objective responses show the potential of nivolumab for treatment of advanced hepatocellular carcinoma [13]. Finally, in future treatment of advanced HCC, it could be highly interesting to not only apply monotherapy but to use combinations of systemic immunomodulation and gene therapy, cell therapy or virotherapy [14,15].

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Endoscopy

Endoscopy remains an important feature in gastroenterology, with an ever growing role for new and adapted classification systems and new techniques that focus on optimising predictors for adenoma and cancer incidence.

High diagnostic performance of EGGIM classification vs OLGIM

Current guidelines (MAPS) suggest that Intestinal Metaplasia (IM) should be staged using OLGIM (Operative Link on Gastric Intestinal Metaplasia), and that patients with stages OLGIM 3 and 4 should be followed-up [1,2]. High-Resolution Narrow-Band Imaging (HR-NBI) was previously shown to be accurate to diagnose IM [3]. Recently a new endoscopic classification (Endoscopic Grading of Gastric Intestinal Metaplasia - EGGIM) has been proposed to assess the risk phenotype of patients by the evaluation of IM in the antrum, and in the corpus with the use of HR-NBI scopes [4,5]. Esposito et al. aimed to determine the accuracy of EGGIM classification, compared with the pathological evaluation of gastric biopsies expressed according to OLGIM classification. A total of 78 adult patients from two centres was included, of which 56% were female, the median age was 61 years, and 8 had a 1st degree family history of gastric cancer. All patients were evaluated by HR White-Light Endoscopy (HR-WLE) followed by HR-NBI. A careful evaluation of the antrum and corpus mucosa was performed followed by the EGGIM score calculation. Five different areas were considered (lesser and greater curvature in the antrum, lesser and greater curvature in the corpus and incisura) and in each area 0 (no IM), 1 (focal IM, less or equal than 30% of the area) or 2 points (extensive IM in that area, more than 30% of the area) were attributed for a total of 10 points. Biopsies were taken where the endoscopists observed IM and, if IM was not present, random biopsies were taken using the updated Sydney System protocol. Subsequently, biopsies from the different sites were sent for histopathologic evaluation in separate jars. The diagnostic performance of EGGIM was then compared to OLGIM (gold standard) using the following criteria: sensibility, specificity, positive predictive value (PPV) and negative predictive value (NPV).

The results showed that IM was staged as OLGIM 0, 2, 3 and 4, respectively: 41.0%, 29.5%, 21.8%, and 7.7% of patients (no patients with OLGIM 1 were found). Compared to OLGIM as gold standard for the evaluation of IM, sensitivity, specificity, PPV and NPV of EGGIM classification were 97.8%, 81.2%, 88.2% and 96.3%, respectively. Three of the 6 patients with false positive results using the EGGIM classification were H. pylori positive. Analysing the subgroup of patients with OLGIM 3 and 4, the diagnostic performance of EGGIM was: sensibility 95.6%, specificity 90.9%, PPV 81.5% and NPV 98.0%. Two of the five patients who resulted false positive using the EGGIM classification were H. pylori positive. In summary, the EGGIM classification showed a high diagnostic performance compared to OLGIM, in particular in patients with OLGIM 3 and 4. A significant correlation between EGGIM and OLGIM scores was observed. A possible confounding factor leading to overestimation of presence of IM might be the presence of H. pylori infection. This approach could be used to simplify the surveillance of these patients [6].

Percutaneous Endoscopic Gastrostomy versus Percutaneous Radiologic Gastrostomy

Currently, gastrostomy is the method of choice for medium and long-term enteral feeding. Available techniques include Percutaneous Endoscopic Gastrostomy (PEG) and Percutaneous Radiologic Gastrostomy (PRG). Although previous studies have compared outcomes between these PRG and PEG, these were limited due to small sample sizes, thus carrying a high risk of confounding and selection bias. Strijbos et al. retrospectively analysed complications and mortality between PEG and PRG procedures in relation to indications. This analysis included adult patients receiving initial PRG (January 2010 until April 2016) and PEG (January 2008 until April 2016). The outcomes were complications (early (≤30 days) and late), success rates and mortality (procedure related, 30-day, and overall). In total, 760 initial procedures (PRG n=469, PEG n=291) were included in the analysis. The mean age of the patients was 62.8 years and the most common indications for PEG or PRG were head and neck malignancy (PEG 38.8%, PRG 69.9%, P=<0.001), CerebroVascular Accident (CVA; PEG 13.7%, PRG 2.1%, P<0.001) and motor neuron disease (PEG 2.7%, PRG 9.8%, P=<0.001). Success rates for placement were 91.2% for PEG (failure mostly due to absence of transillumination) and 97.1% for PRG (P=0.001). Major complications (e.g. abscess, buried bumper, peritonitis) and infections did not differ amongst groups, neither did procedure-related mortality, which was 1.7% in PEG (n=5) vs. 0.4% in PRG (n=2, P=0.113). One case of head and neck tumour seeding occurred after PRG placement. Tube related complications (including dislocation, obstruction, leak and tube defects) were lower in PEG than PRG, both within 30 days (2.7% vs. 26.4% of patients, P=<0.001 and after 30 days (8.6% vs. 31.5%, P=<0.001). The 30-day mortality was higher in patients who received PEG (10.7%) compared to those with PRG (5.1%, P=0.005), with P=0.481 for the multivariate correction. It needs to be noted that the 30-day mortality was more related to the patients' general condition than the procedure itself.

Table 11 Multivariate logistic regression for 30-day mortality [7]

Predictive factors	Odds Ratio (OR for 30-day mortality)
CVA	5.190 (2.139-12.597)
ALS	1.002 (1.001-1.003)
HNC (prophylactic placement)	0.307 (0.212-0.444)

HNC = head and neck cancer; ALS = amyotrophic lateral sclerosis

Overall survival (OS) was 47.87% vs. 43.6% (PEG vs. PRG; P=0.113). Positive predictive factors for OS were PEG, amyotrophic lateral sclerosis and a higher BMI before placement (adjusted OR for all three factors together 1.292 [1.027-1.626]). It was thus concluded that PEG and PRG compare favourably (with PRG yielding a higher initial success rate); PEG is associated with lower frequency of tube-related complications and pain. However, in patients with poor condition or a short life expectancy (e.g. after CVA), neither PEG nor PRG should be performed [7].

Adenoma detection predictors

In a randomised controlled trial, flexible sigmoidoscopy (bowel scope) reduced the ColoRectal Cancer (CRC) incidence and mortality in a population aged 55-64 years [1]. Patients progressed to colonoscopy based on 'high-risk' features [8]. Based on these pivotal findings, the UK Bowel Scope (BS) surveillance program was introduced in 2013 to individuals aged 55. The Wolverhampton Bowel Cancer Screening Centre was the first UK site to fully roll out the program. The correlation between BS findings and subsequent colonoscopy had not previously been evaluated in this specific cohort; this was recently done by Siau et al. by prospectively collecting data from all BS patients in one centre and subsequently identifying those undergoing colonoscopy between August 2013-2016. Conversion rates were assessed as was the compliance with BS protocol and the corresponding endoscopic and histological findings to identify predictors for the detection of pathology at colonoscopy. A total of 11,711 BSs were performed, the adenoma detection rate was 8.5% and the CRC rate was 0.2%. The conversion to colonoscopy in 421 patients was 3.6%. After excluding incomplete colonoscopy or histology,

386 patients were included for the analysis. All patients were aged 55 and 65% was male. The additional adenoma detection rate at colonoscopy was 35.2%, with an additional CRC rate 0.2%. The adenoma miss rate of flexible sigmoidoscopy was 3.6%. On univariate analysis, a polyp ≥10 mm was the only indication associated with increased adenoma detection rate at colonoscopy (OR=2.13, P<0.001). Additional predictors identified included villous (not tubulovillous) histology (OR=4.41, P=0.02), and male gender (OR=2.4 P<0.001). These factors also significantly predicted new ≥10mm adenoma (villous-only histology; OR 6.90 P=0.002 and male gender; OR 3.02 P=0.04). Females with polyps <10mm had the lowest risk of proximal adenomas, whereas men had the highest risk (Table 12). Further analyses as well as larger studies are now required to clarify the benefits of converting low-risk tubulovillous adenomas at BS to colonoscopy [9].

Table 12 Prediction models for detecting proximal adenoma based on gender and polyp size at flexible sigmoidoscopy [9]

		Adenoma			Adenoma ≥10mm		
Grouping	**N**	**ADR**	**OR (95%CI)**	***P***	**ADR**	**OR (95%CI)**	***P***
Female; polyp <10mm	66	15.2%	Reference		1.5%	Reference	
Female; polyp ≥10mm	70	31.4%	2.6 (1.1-6.0)	0.003*	4.3%	2.9 (0.3-29)	0.65
Male; polyp <10mm	124	33.1%	2.8 (1.3-6.0)	0.01*	4.0%	2.7 (0.3-24)	0.61
Male; polyp ≥10mm	126	50.8%	5.8 (2.7-12)	<0.001*	12.7%	9.5 (1.2-73)	0.02

Continuous warfarin use within therapeutic range better than HBT in endoscopic surgery

Heparin Bridging Therapy (HBT) is recommended for patients on anticoagulants that have a high-thrombotic risk and who are undergoing a high-bleeding risk procedure such as endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) [10,11]. However, HBT is related to the high frequency of delayed bleeding [12,13]. A Japanese study analysed bleeding and coagulation markers in the management of anticoagulants without HBT, during the perioperative periods of ESD and EMR. Patients who underwent ESD or EMR and received warfarin or a Direct Oral AntiCoagulant (DOAC) during the period from January 2013 to March 2017 were analysed. Generally, administration of warfarin was continued within the therapeutic range of the international normalised ratio during the perioperative periods and DOACs were not administered on the day of the procedure. HBT was conducted only for patients who had a hypercoagulable condition. The rates of delayed bleeding in patients who received warfarin and patients who received DOACs were compared, and coagulation molecular markers including soluble fibrin, thrombin-antithrombin complex (TAT), prothrombin fragment 1+2 (F1+2) and D-dimer were compared before and after the procedures in 13 patients who received DOACs. Among the patients who underwent ESD or EMR during the study period, 51 patients received warfarin and 49 received DOACs. Delayed bleeding occurred in 11.8% in the warfarin group and in 16.3% in the DOAC group; no significant difference was observed (P=0.573). Only 1 patient with continued administration of antiplatelet agents had delayed bleeding among the patients in whom administration of warfarin was continued within the therapeutic range (5.3%, 1/19). Fifteen percent of the 40 patients in the DOAC group for whom the DOAC was not administered on the day of the procedure had delayed bleeding, while 23.8% of the patients who received HBT had delayed bleeding. No thrombotic events occurred from 1 month after the procedures. One patient in whom the DOAC was not administered on the day of the procedure became positive for TAT, F1+2 and D-dimer after EMR and had a hypercoagulable condition. Thus, for perioperative management of anticoagulants in patients undergoing ESD or EMR, continuous use of warfarin within the therapeutic provides a lower risk of delayed bleeding. However, DOACs should be carefully managed with attention to haemorrhagic risks and coagulable conditions [14].

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